EFFECTS OF RADIATION DOSE AND VOLUME TO THE LARYNX

IN INTENSITY MODULATED RADIATION THERAPY

OF NON-LARYNGEAL HEAD AND NECK MALIGNANCIES

DEPARTMENT OF RADIATION ONCOLOGY,
CHRISTIAN MEDICAL COLLEGE,
VELLORE, TAMIL NADU 632004

DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF
MD – RADIOTHERAPY (BRANCH IX)
EXAMINATION MAY 2019

Certificate

This is to certify that the dissertation entitled "**Effects of Radiation Dose and Volume to the Larynx in Intensity Modulated Radiation Therapy of non-laryngeal head and neck malignancies**" is a bonafide work done by Dr Nikhil S, Post Graduate Student in the Department of Radiation Oncology, Christian Medical College, Vellore during the period from April 2016 to April 2019 and is being submitted to The Tamil Nadu Dr M. G. R Medical University in partial fulfilment of the MD Branch Radiotherapy examination conducted in May 2019.

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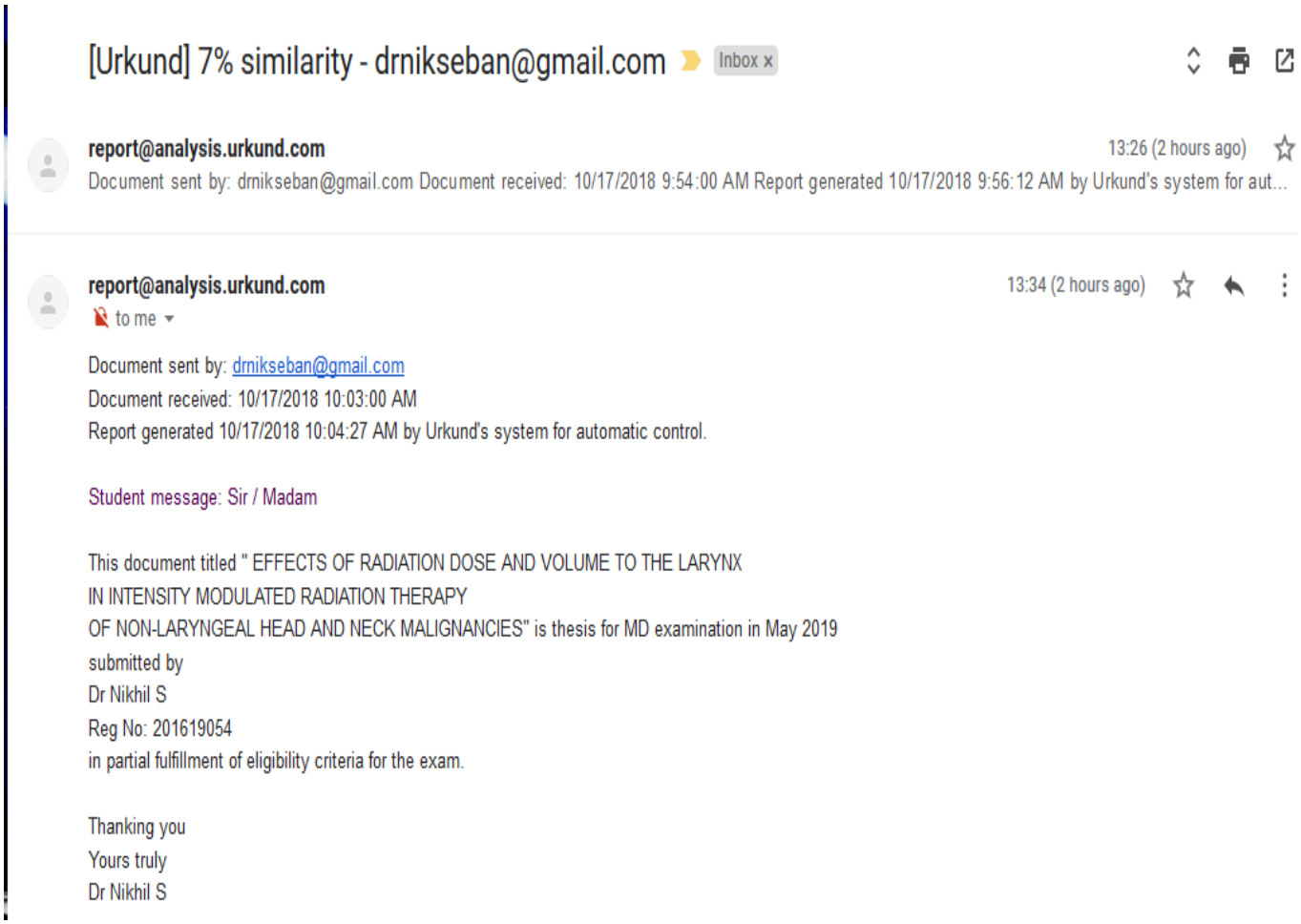

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in partial fulfillment of eligibility criteria for the exam.

Thanking you
Yours truly
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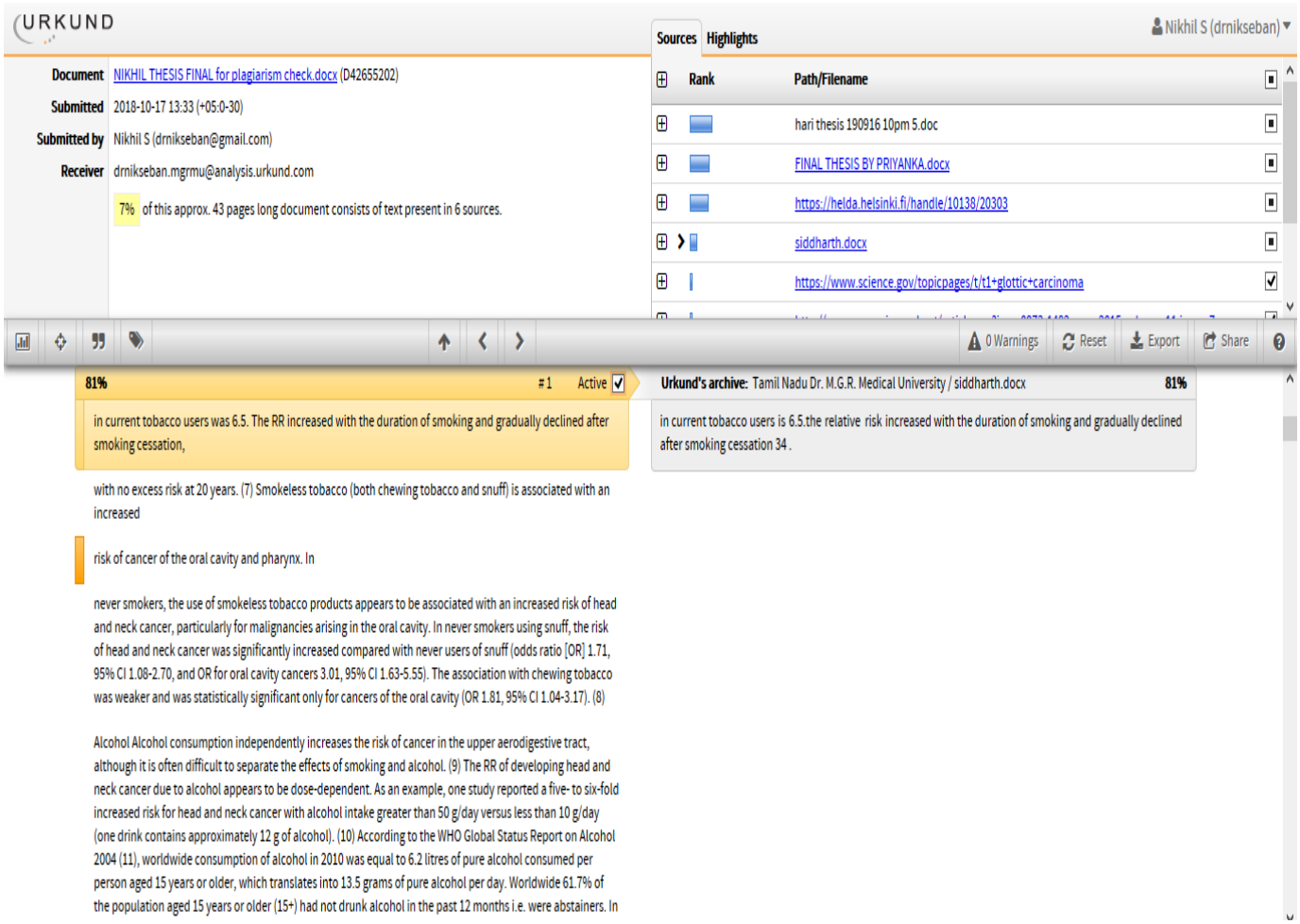
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in current tobacco users was 6.5. The RR increased with the duration of smoking and gradually declined after smoking cessation,
with no excess risk at 20 years. (7) Smokeless tobacco (both chewing tobacco and snuff) is associated with an increased
risk of cancer of the oral cavity and pharynx. In
never smokers, the use of smokeless tobacco products appears to be associated with an increased risk of head and neck cancer, particularly for malignancies arising in the oral cavity. In never smokers using snuff, the risk of head and neck cancer was significantly increased compared with never users of snuff (odds ratio [OR] 1.71, 95% CI 1.08-2.70, and OR for oral cavity cancers 3.01, 95% CI 1.63-5.55). The association with chewing tobacco was weaker and was statistically significant only for cancers of the oral cavity (OR 1.81, 95% CI 1.04-3.17). (8)
Alcohol Alcohol consumption independently increases the risk of cancer in the upper aerodigestive tract, although it is often difficult to separate the effects of smoking and alcohol. (9) The RR of developing head and neck cancer due to alcohol appears to be dose-dependent. As an example, one study reported a five- to six-fold increased risk for head and neck cancer with alcohol intake greater than 50 g/day versus less than 10 g/day (one drink contains approximately 12 g of alcohol). (10) According to the WHO Global Status Report on Alcohol 2004 (11), worldwide consumption of alcohol in 2010 was equal to 6.2 litres of pure alcohol consumed per person aged 15 years or older, which translates into 13.5 grams of pure alcohol per day. Worldwide 61.7% of the population aged 15 years or older (15+) had not drunk alcohol in the past 12 months i.e. were abstainers. In
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81%
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Abstract

Objectives: To assess the effects of radiation dose and volume parameters to the larynx by assessing the mucosal reactions with flexible laryngoscopy and its correlation with voice-related quality of life using V-RQOL questionnaire, in patients undergoing Intensity-modulated radiation therapy for non-laryngeal head and neck malignancies. *Methods*: DVH dose and volume parameters including D_{max}, D_{mean}, V_5 to $V_{73.5}$ were obtained. Patients underwent flexible laryngoscopy prior to, during and at the completion of radiation therapy, and laryngeal oedema was graded as per RTOG grading criteria. The V-RQOL questionnaire was administered at same time points, and QOL scores including total, socioemotional and physical subdomains were calculated. *Results:* Among the total of 31 patients, two and six of them had grade 2 oedema midway during and at the end of radiation therapy respectively. Ten (32.3%), eight (25.8%) and ten (32.3%) patients had a V-RQOL total, socio-emotional and physical scores less than 75 at midway assessment respectively. But this increased to 17 (54.8%), 15 (49.4%) and to (83.9%) at the end of radiation therapy respectively. There was a significant correlation of V_{65} with laryngeal oedema; and V60, V65 and V70 with the total V-RQOL score at the end of RT, V_5 to V_{70} with socioemotional V-RQOL and V_{65} with the physical domain of the V-RQOL score. OAR constraints for larynx in IMRT could be V60 <1% for grade 2 laryngeal oedema, and V65< 1% for V-RQOL to be less than 75 at the end of radiation therapy. *Conclusion:* OAR constraints for larynx in IMRT could be V60 <1% for grade 2 laryngeal oedema, and V65< 1% for V-RQOL to be less than 75 at the end of radiation therapy.

Keywords: IMRT, voice-related quality of life, laryngeal oedema, V-RQOL questionnaire.

Introduction

The patients with non-laryngeal head and neck carcinomas receive radiation therapy to the neck for treating the draining lymph nodal groups, which were involved clinically or as elective neck irradiation. The radiation dose required for tumour control would cause acute and late normal tissue effects in the form of dermatitis, mucositis, xerostomia, dysphonia and dysphagia. Radiation received to the larynx during irradiation of other head and neck primary tumours and/or elective neck irradiation results in oedema of the larynx. This affects the voice quality of the patient to a varying extent. This limits the patients' quality of life and handicaps them in personal and professional spheres of life. There are different interview based and self-administered questionnaires to assess the voice-related quality of life.

Intensity-modulated radiation therapy (IMRT) has a definite advantage in head and neck cancers, in that the treatment can be accurately delivered because it results in relative sparing of normal structures such as parotid glands, and also organ motion is virtually absent with proper immobilization. There is limited data about the dose and volume limits of radiation to the larynx. With the notable exception of the parotid glands, the available clinical data do not allow an accurate definition of dose-volume objectives for most other OARs in the head-and-neck region. If the values of dose-volume parameters to keep the incidence of laryngeal oedema to the minimum in IMRT of non-laryngeal head and neck malignancies can be defined, it can be utilized to maximally improve the voice quality in these patients.

Aims

To assess the effects of radiation dose and volume to the larynx and quality of life in intensity modulated radiation therapy for non-laryngeal head and neck malignancies.

Objectives

Primary objective

- To assess the effects of radiation dose and volume parameters to the larynx in patients undergoing Intensity modulated radiation Therapy for non-laryngeal head and neck malignancies by assessing the mucosal reactions with flexible laryngoscopy.

Secondary objective

- To assess the Quality of Life in patients undergoing Intensity Modulated Radiation therapy for non-laryngeal head and neck cancers using Voice-related quality of life (V-RQOL) questionnaire and its relation with dose-volume parameters.

Literature review

Head and neck malignancies

Incidence and prevalence

World scenario

Head and neck cancer account for more than 550,000 cases and 380,000 deaths annually worldwide(1). In the United States, head and neck cancer accounts for 3 per cent of malignancies, with approximately 63,000 Americans developing head and neck cancer annually and 13,000 dying from the disease(2). In Europe, there were approximately 250,000 cases (an estimated 4 per cent of the cancer incidence) and 63,500 deaths in 2012 (3).

Male to female ratio ranges from 2:1 to 4:1. About 90% of all head and neck cancers are squamous cell carcinomas (HNSCC). HNSCC is the sixth leading cancer by incidence worldwide. Most HNSCCs arise in the epithelial lining of the oral cavity, oropharynx, larynx and hypopharynx. The incidence of malignancies of oral cavity, nasopharynx, oropharynx and larynx are 2.1%, 0.6%, 1.0% and 1.1% respectively as per the GLOBOCAN 2012 data for both sexes worldwide(4). Oral cavity cancers are the most common with oral tongue. Laryngeal cancer is the second most common Head and Neck Cancer with >1, 59, 000 new cases and 90,000 cancer deaths worldwide and it forms 2% of all cancers.

Indian scenario

The head and neck squamous cell carcinomas account for one-third of cancers in our country. According to the Indian Council of Medical Research (ICMR), 0.2 to 0.25 million patients are diagnosed each year with head and neck cancers (5). The prevalence rates of head and neck cancers in India as reported by GLOBOCAN 2012 is very high. The prevalence rates of Lip & Oral cavity cancers, larynx, nasopharynx, other pharynx were 12.6%, 6.8%, 1.1% and 7% respectively. This shows the high burden of head and neck cancers in India with 5-year prevalence rates of nearly 27 per cent.

Oral cavity:

India has a much higher incidence of oral cavity cancer as compared to the western world. Age-standardized incidence rates in India is 7.5 per 100,000 population, but in Europe and USA, it is 4.6 and 3.8 per 100,000 respectively. Among the different sites, oral cavity cancer is the leading cause of cancer-related mortality in India, especially in men accounting for 22.9%. As the subsite of the oral cavity, the oral tongue is the most common site in the rest of the world, but in India gingivobuccal complex is most common. (6). The males of Ahmedabad urban showed highest Age-Adjusted Rate (AAR) for mouth cancer (12.9) followed by Bhopal (9.9). For females, however, Bengaluru showed the highest AAR (6.5) followed by Kamrup urban district (5.8).

Laryngeal cancer:

In males, East Khasi Hills District (11.1) had the highest Age-adjusted rate (AAR) in laryngeal cancers followed by Aizawl District (9.5) and Kamrup urban District, in Assam (8.2).

Hypopharynx:

In males, the AARs of hypopharyngeal cancers in East Khasi Hills District of Meghalaya was 21.5 and the state of Meghalaya as a whole was 17.4, which were higher followed by Aizawl District (15.4) of Mizoram. In females, Kamrup Urban District (Assam) showed the highest AAR (3.6) followed by Cachar District (Assam) (2.6).

Table 1: Number of registered cancer cases in different cancer registries throughout India and the proportion of Head and Neck Cancers

Registry		**Males**			**Females**	
	All sites	Number of Head and Neck cancers	Proportion of Head and Neck cancers (%)	All sites	Number of Head and Neck cancers	Proportion of Head and Neck cancers (%)
Mumbai	22580	6805	30.1	18528	1673	9.0
Bangalore	11273	3532	31.3	13125	1822	13.9
Chennai	15731	4427	28.1	17499	1832	10.5
Thiruvananthapuram	19219	4798	25.0	18809	1726	9.2
Dibrugarh	2895	1211	41.8	2276	329	14.5
Guwahati	6803	2830	41.6	4679	702	15.0
Chandigarh	2643	598	22.6	2092	100	4.8
Total	**81144**	**24201**	**29.8**	**77008**	**8184**	**10.6**

Aetiology

The most commonly linked risk factors to head and neck cancer are tobacco use, alcohol consumption, human papillomavirus (HPV) infection (for oropharyngeal cancer), and Epstein-Barr virus (EBV) infection (for nasopharyngeal cancer). This, in long-term, leads to the development of head and neck malignancies. The relative prevalence of these risk factors in different parts of the world explains the differences in the incidence of subsites of head and neck cancer in each area.

Tobacco

Tobacco use may be either in the smoked form or smokeless tobacco. The smoked tobacco may be in the form of cigarettes, cigars, pipes, bidis and hukkas. There are other forms of smokeless tobacco which have high consumption rates and form a major causative agent for head and neck malignancies. Commonly used tobacco products are chewing tobacco, moist snuff, pan or betel quid and gutkha. All these tobacco products have been found to have carcinogens and have been implicated in the causation of a large number of malignancies including head and neck malignancies. The relative risk (RR) in current tobacco users was 6.5. The RR increased with the duration of smoking and gradually declined after smoking cessation, with no excess risk at 20 years. (7)

Smokeless tobacco (both chewing tobacco and snuff) is associated with an increased risk of cancer of the oral cavity and pharynx. In never smokers, the use of smokeless tobacco products appears to be associated with an increased risk of head and neck cancer, particularly

for malignancies arising in the oral cavity. In never smokers using snuff, the risk of head and neck cancer was significantly increased compared with never users of snuff (odds ratio [OR] 1.71, 95% CI 1.08-2.70, and OR for oral cavity cancers 3.01, 95% CI 1.63-5.55). The association with chewing tobacco was weaker and was statistically significant only for cancers of the oral cavity (OR 1.81, 95% CI 1.04-3.17). (8)

Alcohol

Alcohol consumption independently increases the risk of cancer in the upper aerodigestive tract, although it is often difficult to separate the effects of smoking and alcohol. (9) The RR of developing head and neck cancer due to alcohol appears to be dose-dependent. As an example, one study reported a five- to six-fold increased risk for head and neck cancer with alcohol intake greater than 50 g/day versus less than 10 g/day (one drink contains approximately 12 g of alcohol). (10)

According to the WHO Global Status Report on Alcohol 2004(11), worldwide consumption of alcohol in 2010 was equal to 6.2 litres of pure alcohol consumed per person aged 15 years or older, which translates into 13.5 grams of pure alcohol per day. Worldwide 61.7% of the population aged 15 years or older (15+) had not drunk alcohol in the past 12 months i.e. were abstainers. In 2012, about 3.3 million deaths, or 5.9% of all global deaths, were attributable to alcohol consumption.

As per the 2003 National Household Survey of Alcohol and Drug Abuse(12)in India of 40,697 males aged between 12 to 60 years revealed that 74.1% of the sampled population was lifetime abstainers. 21.4% were reported to be current users of alcohol (used in the last 30

days)(13). Prevalence was approximately 23% among adults and the older age group (30 years and above) and 4.2% among adolescents and young adults (10 to 29 years). Alcohol intake and tobacco smoking appear to have an interactive and multiplicative effect on the risk of developing head and neck cancer. (14)

Betel nut chewing

Betel nut chewing, which is widespread in certain regions of Asia, is an independent risk factor for the development of squamous cell head and neck cancer. The effects appear to be synergistic with tobacco and alcohol. (15)

Preparation of betel quid which is chewed varies between places. In Southcentral Asia, betel quid is chewed along with tobacco mostly, whereas in other parts of Asia it is used without tobacco. The contents are areca nut (Areca catechu), along with slaked lime (calcium oxide and calcium hydroxide), which is wrapped in the leaf of Piper betel plant with other condiments and spices.

A meta-analysis of all studies about the impact of betel nut chewing with or without tobacco on head and neck and oesophagal cancers in Asia reported that the relative risk of oral cavity and oropharyngeal cancers for betel quid with tobacco was 77.4 and without tobacco was 2.56.

Viral infections

Multiple types of viral infections have been associated with an increased risk of head and neck cancer, including particularly EBV, HPV, and human immunodeficiency virus (HIV).

EBV association with nasopharyngeal cancers

EBV has been well established as an etiologic factor in the pathogenesis of nasopharyngeal carcinoma(16).

Epithelial infection of EBV may not be the initiating event in the pathogenesis of nasopharyngeal cancer. There are a few genetic changes which predispose to subsequent EBV infection like 3p and 9p deletions, and possibly environmental factors such as dietary consumption of smoked or salted fish. Stable EBV infection of epithelial cells requires an altered, undifferentiated cellular environment and that cyclin D1 overexpression (a consequence of p16 deletion on chromosome 9p and amplification of the cyclin D1 locus on chromosome 11q) facilitates persistent EBV infection of immortalized nasopharyngeal epithelial cells.

Nasopharyngeal carcinoma cells express a specific subgroup of EBV-latent proteins, including EBNA-1 and two integral membrane proteins, LMP-1 and LMP-2, which may be used for confirmation of EBV. Alternatively, EBV DNA detection by PCR can be done.

Smoking may be involved in the pathogenesis of nasopharyngeal carcinoma by causing EBV reactivation(17).

HPV-association with Oropharyngeal cancers(18)

Despite the prevalence of smoking and in turn the overall incidence of head and neck cancers decreasing over the past two decades, the oropharyngeal cancer incidence was steadily increasing. This is particularly in the base of the tongue and tonsil subsites, where the incidence has increased by 2-3% annually during 1973-2001, and then by 5.22% annually from 2000 to 2004 in the USA. Similar trends are observed in other countries also. Approximately 50 per cent of oropharyngeal cancers were attributable to HPV. The timing between exposure to HPV and the development of oropharyngeal cancer probably exceeds 10 years(19).

HPV-positive patients are mostly younger with a median age of 54 years at diagnosis, with less history of use of tobacco and alcohol and higher socioeconomic status and education. In the USA, HPV is less prevalent in blacks as compared to the white population. Also, HPV-positive tumours present typically with early T stage (T1-T2) and higher N stage (usually cystic and multilevel), lesser incidence of metastases, and with a distinct pattern than HPV negative tumours. They have distinct histological features, such as moderate/poor tumour differentiation and non-keratinizing or basaloid pathology. The HPV-positive oropharyngeal cancer had a 28% reduction in the risk of death and a 49% reduction in the risk of disease recurrence and has a better prognosis than HPV negative oropharyngeal cancers. (20)

The most common high-risk HPV types are HPV16, HPV18, HPV31, HPV33 and HPV35. These types are estimated to cause about 5% of the cancer burden worldwide, which includes about 25%–60% of head and neck cancers among other sites.

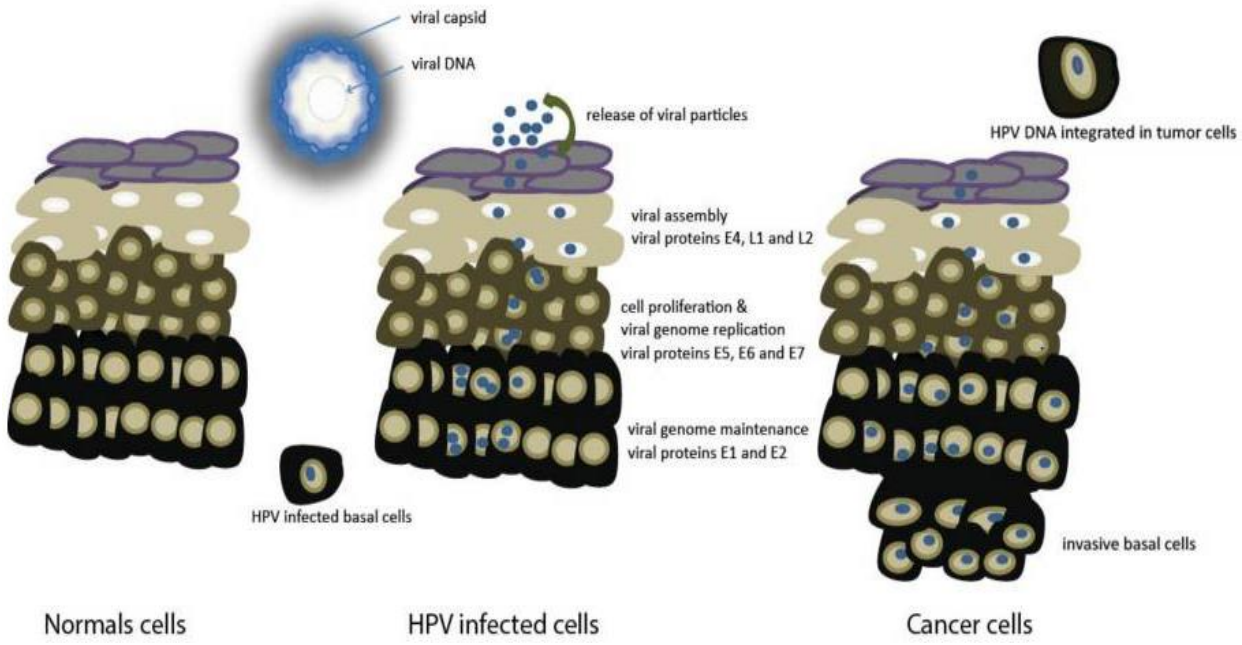
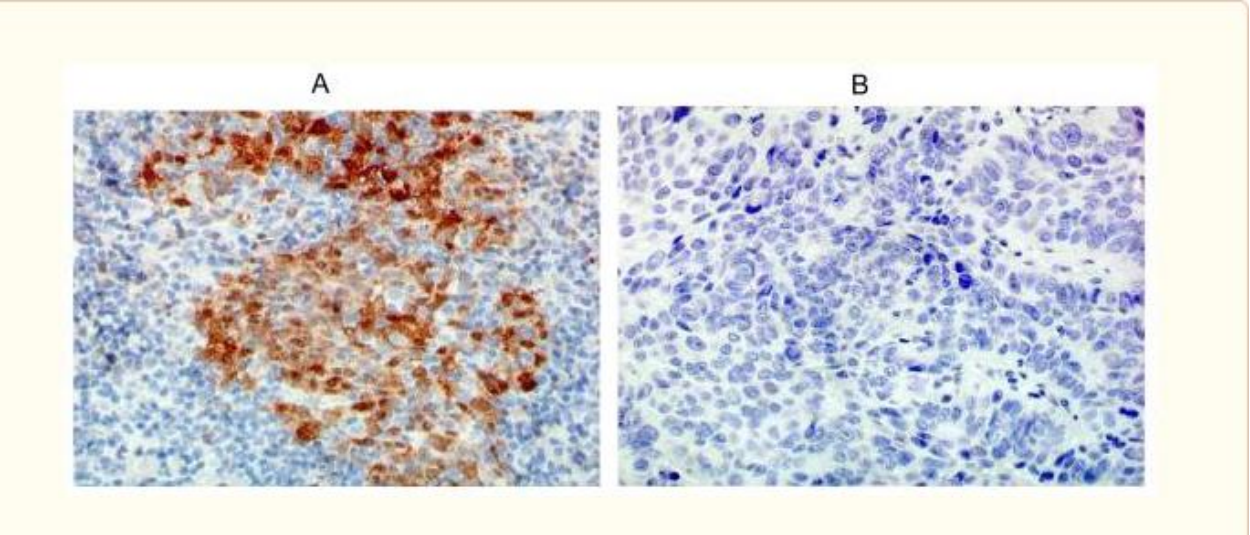


Figure (i): HPV induced carcinogenesis

Most of the low-grade HPV infections are cleared off by the body. The high-grade infections or the long lasting ones result in viral DNA integration into the host genome. It starts with the destruction of E2 gene and higher expression of the oncogenes E6 and E7 in basal layer leading to a disruptive viral infection and incomplete viral life cycle and causes disruption of the cell cycle checkpoints.

Degradation of pRB protein by E7 will result in activation of elongation factor (E2F) and subsequent transcription of S phase genes. The uncontrolled transcription of S phase genes also leads to the expression of p16INK4a (encoded by CDKN2A), a CDK inhibitor, as a negative feedback loop, which is also used as surrogate marker for HPV infections. E6 binds to E3 ubiquitin ligases and results in degradation of TP53, which leads to cell cycle deregulation, due to loss of p21 function (CDK inhibitor) and loss of TP53 mediated apoptosis.

P16 is used as a surrogate marker of HPV infection. It is tested using immunohistochemistry and has good sensitivity for HPV positive oropharyngeal cancers. (21)



***Fig(ii)**: **p16 by IHC (**A) Case 1 shows brown nuclear and cytoplasmic staining indicating p16 positive status; (B) Case 2 shows no staining indicating p16 negative status. 40X magnification. (IHC - immunohistochemistry)*

HPV association with Non-oropharyngeal cancers:

A systematic review and meta-analysis identified 148 studies, including 12,163 cases of squamous cell carcinoma of the head and neck. The HPV prevalence rates in oropharyngeal, oral cavity, and laryngeal cancers were 45.8, 24.2, and 22.1 per cent, respectively, and the prevalence rates of HPV-16 positivity were 40.6, 14.9, and 13.4 per cent, respectively(22). The presence of HPV-16 in the oral cavity has been associated with the subsequent development of oropharyngeal carcinoma.

HIV

HPV related oropharyngeal carcinoma, EBV-related SCC and LEC of salivary gland origin, NPC are non-AIDS defining malignancies. With the use of highly active antiretroviral therapy (HAART) an increased survival of these patients, there is an increased prevalence of these AIDS-associated malignancies. This is also attributed to increased CD4 counts due to HAART and direct oncogenic effect of HIV. There is an approximately two- to threefold increase in the incidence of SCC of the head and neck in patients infected with HIV; other histologic types of cancer may also be increased(23,24).

Occupational exposure:

The agents with a potential relationship with head and neck cancer include the dry cleaning agent perchloroethylene, asbestos, pesticides, man-made mineral vitreous fibres (MMMF), polycyclic aromatic hydrocarbons. Textile workers, woodworkers, manufacturers of mustard gas, plastic and rubber products, naphthalene refiners, ethanol, sulfuric acid mist, leather and paint workers, automobile mechanics, construction workers (cement), farmers, and metal workers are at increased risk for head and neck cancers. Formaldehyde was classified as a carcinogen in 2004 because of its association with nasopharyngeal cancer and possibly cancers of the nasal cavity and paranasal sinuses. SCCs of the larynx and the base of the tongue have also been associated with exposure to Agent Orange. (25)

Radiation

Prior irradiation for either malignant or benign disease has been linked to thyroid cancer, salivary gland tumours, SCCs, and sarcomas. Although this relationship appears to be real, there is a long latency period, and the overall risk is low. (25)

Occupational exposure to radiation has also been linked to carcinogenesis. INWORKS study(26) showed a linear increase in the rate of cancer with increasing radiation exposure. The excessive relative rate per Gy for death was 0.51. The estimated rate of mortality from all cancers excluding leukaemia increased with cumulative dose by 48% per Gy (90% confidence interval 20% to 79%), lagged by 10 years.

Diet

Frequent consumption of salted fish, smoked or preserved meats that contain high levels of added nitrites have an 80% increased risk of developing nasopharyngeal carcinoma(27).

Genetic factors

Patients with Fanconi anaemia are at high risk for developing a malignancy, including SCC of the head and neck, myelodysplastic syndrome, and acute myelocytic leukaemia. Head and neck cancers in these patients tend to arise at an earlier age and in the absence of other risk factors (tobacco, alcohol)(28). 3% of Fanconi anaemia patients had head and neck malignancy(29). The management of patients with head

and neck cancer arising with Fanconi anaemia is complicated by the significant increase in susceptibility to complications of radiation therapy(30).

Anatomical sites and subsites of head and Neck cancer

The major sites include (1) the oral cavity, (2) the oropharynx, (3) the hypopharynx, (4) the larynx, (5) the nasopharynx, and (6) the nose and paranasal sinuses. These sites and the sub-sites are depicted in Figure-1.

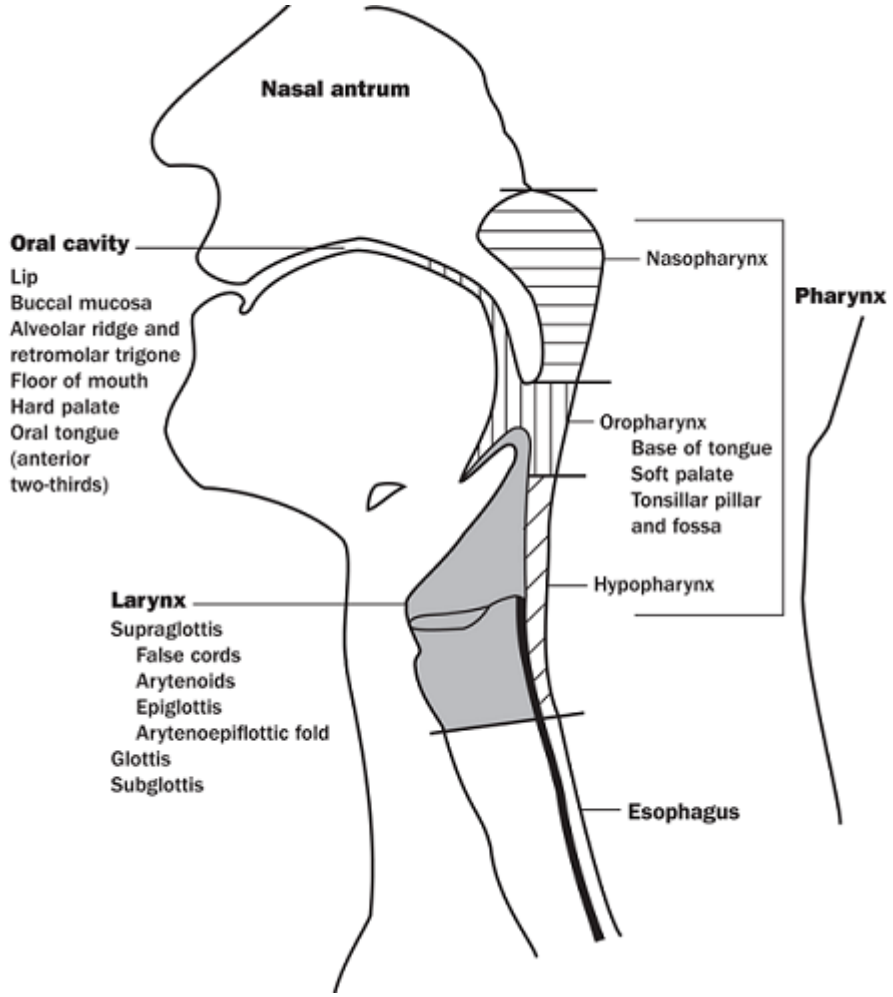


Figure (iii): **Depicting various sites and sub-sites of Head and Neck epithelial malignancies.**

The sites and subsites as listed in AJCC 8th edition is as follows:

Lip

1. External upper lip (vermilion border)

2. External lower lip (vermilion border)

3. Commissures

Oral Cavity

1. Buccal mucosa

a. Mucosa of upper and lower lips

b. Cheek mucosa

c. Retromolar areas

d. Buccoalveolar sulci, upper and lower (vestibule of mouth)

2. Upper alveolus and gingiva (upper gum)

3. Lower alveolus and gingiva (lower gum)

4. Hard palate

5. Tongue

a. Dorsal surface and lateral borders anterior to vallate papillae (anterior two thirds)

b. Inferior (ventral) surface

6. Floor of mouth

Oropharynx

1. Anterior wall (glossoepiglottic area)

a. Base of the tongue (posterior to the vallate papillae or posterior third)

b. Vallecula

2. Lateral wall

a. Tonsil

b. Tonsillar fossa and tonsillar (faucial) pillars

c. Glossotonsillar sulci (tonsillar pillars)

3. Posterior wall

4. Superior wall

a. The inferior surface of soft palate

b. Uvula

Nasopharynx

1. Posterosuperior wall: extends from the level of the junction of the hard and soft palates to the base of the skull

2. Lateral wall: including the fossa of Rosenmüller

3. Inferior wall: consists of the superior surface of the soft palate

Histology

The WHO working group on Head and Neck tumours published classification for tumours of head and Neck in 2003. The most common type is the malignant epithelial tumours which include Squamous cell carcinoma, Verrucous carcinoma, Basaloid squamous cell carcinoma, Papillary squamous cell carcinoma, Spindle cell carcinoma, Acantholytic squamous cell carcinoma, Adenosquamous carcinoma, Lymphoepithelial carcinoma and Giant cell carcinoma. Salivary gland-type tumours include mucoepidermoid carcinoma and adenoid cystic carcinoma, and adenomas which are pleomorphic adenoma and oncocytic papillary cystadenoma. Other classes of tumours include neuroendocrine tumours, soft tissue and bone sarcomas, lymphomas, mucosal malignant melanomas and other benign tumours.

Nasopharyngeal carcinoma has been classified by WHO classification of Head and Neck tumours published in 2017 as follows:

1. Nasopharyngeal carcinoma

a. Non-keratinizing squamous cell carcinoma

(i) Undifferentiated

(ii) Differentiated

b. Keratinizing squamous cell carcinoma

(i) Well-differentiated carcinoma

(ii) Moderately differentiated carcinoma

(iii) Poorly differentiated carcinoma

c. Basaloid squamous cell carcinoma

2. Nasopharyngeal papillary adenocarcinoma

3. Salivary gland-type tumours.

Diagnostic evaluation

The evaluation includes a detailed history and physical examination including a thorough head and neck examination. Clinical examination of the primary involves assessing the type of lesion (proliferative, infiltrative), extent and involvement of underlying structures. Examination under anaesthesia (EUA) is also performed for deep lesions that are difficult to assess.

FNAC/ biopsy

Fine needle aspiration cytology (FNAC) is done when there are palpable neck nodes. The sensitivity is 85 to 90%. Non-diagnostic aspirations and poor yield occur when the nodes are cystic, more common in HPV positive oropharyngeal cancers.

Nasopharyngolaryngoscopy

Nasopharyngolaryngoscopy is done for diagnosis of nasopharyngeal, laryngeal and hypopharyngeal tumours. The size and location of the lesion can be described, and biopsy from the lesion can be taken for histological diagnosis.

In Direct Laryngoscopy, a flexible fibre optic laryngoscope is inserted through the mouth or nose to evaluate the larynx, for mobility of the vocal cords or any mucosal lesions. In Indirect Laryngoscopy, an IDL mirror is used to view an inverted image of the larynx and the surrounding structures.

Ultrasound

Metastatic lymph nodes in head and neck cancers are site-specific and depend on the location of the primary tumours most often. USG helps in the identification of metastatic nodes with the help of certain identifying features. Size of the node helps to distinguish between reactive and malignant node. Generally, malignant nodes tend to be larger than the reactive nodes. In head and neck malignancy nodes more than 10mm are considered to be significant according to size criteria. Nodes with rounded shape with the short axis to long axis diameter more than 0.5 are more likely to be malignant. Eccentric cortical hypertrophy due to focal tumour infiltration is also a

diagnostic feature of malignant neck nodes. The borders of malignant nodes are sharp, and they are usually hypoechoic and may have calcifications. Although matting is a typical feature of tuberculosis, it is also seen in advanced malignancies.

CT and MRI

Computerized tomography is the mainstay for imaging head and neck cancers. Most centres acquire axial CT images from skull base to diaphragm. (31)The advantage of CT is its spatial resolution, but at the cost of radiation exposure, and is excellent in bony detail such as mandibular or skull base involvement. The disadvantage of CT is insufficient soft tissue characterization for imaging the tongue primary and preferably is to be used when MRI not available. If CT is done then contrast-enhanced CT is mandatory; performed after injection of 50-80 ml low osmolar non-ionic iodine-containing contrast; CT images to be viewed at high contrast settings. Multidetector CT with multiplanar reformations (at least 16 slice scanner)is preferred. Images of both soft tissue and bone window are preferable to be viewed axially and with coronal reformation to assess extrinsic muscles, mandible and neurovascular bundle. CT is the most specific modality for mandibular erosion with high positive predictive value. However mandibular invasion is infrequent in tongue cancers, seen in< 10%, i.e. in advanced cancers or bulky tumours reaching or involving floor of the mouth.

MRI T1-weighted ‘anatomical’ images have an excellent spatial resolution, while T2-weighted images preferentially highlight oedema and therefore pathology. STIR images suppress the surrounding fat and have the capability of enhancing oedema or the pathology as a more bright signal than the conventional T2 images.

MRI is the imaging method of choice due to superior soft tissue characterization and when performed optimally provides accurate information regarding staging and tumour thickness. A tumour to normal tongue contrast is maximum on contrast-enhanced T1W sequences that help to achieve accurate staging. MRI is very sensitive for mandibular erosion and has high negative predictive value, but can overestimate cortical erosion due to chemical shift artefacts. Nodal status is studied with a combination of T2W, STIR and post-gadolinium sequences but adding diffusion-weighted imaging (if available) can increase the accuracy of the nodal status evaluation. The features of nodes that can be appreciated in MRI are:

1. Number & size of abnormal nodes
2. Level of abnormal nodes
3. Ipsilateral, contralateral or bilateral
4. Presence of necrosis
5. Evidence of extra-capsular spread
6. Invasion of adjacent structures and vessels (circumferential contact with ICA/CCA)

There are two meta-analyses showing the equivalence of ultrasound, CT and MRI in the detection of nodal metastases. Few studies exist comparing CT and MRI for imaging the oral cavity with emphasis on tongue cancers. MRI is favoured over CT for T staging (better soft tissue delineation) particularly for tongue and floor of mouth squamous cancers while CT and MRI were comparable for N staging.

PET CT

PET CT, performed with 18- fluorodeoxyglucose as the tracer is most commonly used.

(1) The upfront indication is in the evaluation of a neck node with unknown primary.
(2) It can be used for staging head and neck cancers at diagnosis i.e. in evaluating distant metastases in stage III & IV tongue cancers particularly with large nodes in the lower neck. It can depict the extent of nodal involvement in the N+ neck but has no role in the evaluation of the N0 neck.
(3) PET also has a role in post RT setting to distinguish between recurrence and post RT changes or necrosis.
(4) The role in following up patients after treatment is not yet recommended according to 2013, the Royal College of Radiologists' evidence-based guidelines. (32)

Staging of head and neck cancer

The staging of Head and Neck cancers follow the TN staging 8th edition(33)published by the American Joint Committee on Cancer (AJCC). Three categories comprise the system: T—the characteristics of tumour at the primary site (this may be based on size, location, or both); N—the degree of regional lymph node involvement; and M—the absence or presence of distant metastases. The specific TNM status of each patient is then tabulated to give a numerical status of Stage I, II, III, or IV. Specific subdivisions may exist for each stage and may be denoted with a, b, or c status. T4a

disease indicates *moderately advanced disease* and is specific by subsite, but is still considered resectable. T4b disease is *very advanced disease* with findings— such as carotid artery encasement, prevertebral involvement, and skull base involvement— that previously determined the disease to be unresectable. In general, the early-stage disease is denoted as Stage I or II disease, and advanced stage disease as Stage III or IV disease. Of importance is that any positive metastatic disease to the neck will classify the disease as advanced, except in select nasopharynx and thyroid cancers. T4a disease is staged as IVa. T4b disease is staged as IVb, and any distant metastasis is staged as IVc.

Detailed staging of carcinomas of the oral cavity, oropharynx and nasopharynx is as follows:

Oral cavity tumours

T staging

T1- Tumour 2 cm or less in greatest dimension and 5 mm or less depth of invasion

T2- Tumour 2 cm or less in greatest dimension and more than 5 mm but no more than10 mm depth of invasion or Tumour more than 2 cm but not more than 4 cm in greatest dimension and depth of invasion no more than 10 mm

T3- Tumour more than 4 cm in greatest dimension or more than 10 mm depth of invasion

T4a *(Lip)* Tumour invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin (of the chin or the nose)

T4a *(Oral cavity)* Tumour invades through the cortical bone of the mandible or maxillary sinus or invades the skin of the face

N staging

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension without extranodal extension

N2 Metastasis described as:

N2a Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension without extranodal extension

N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, without extranodal extension

N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension, without extranodal extension

N3a Metastasis in a lymph node more than 6 cm in greatest dimension without extranodal extension

N3b Metastasis in a single or multiple lymph nodes with clinical extranodal extension (The presence of skin involvement or soft tissue invasion with deep fixation/tethering underlying muscle or adjacent structures or clinical signs of nerve involvement is classified as a clinical extranodal extension. Midline nodes are considered ipsilateral nodes)

M – Distant Metastasis

M0 No distant metastasis

M1 Distant metastasis

pN – Regional Lymph Nodes

Histological examination of a selective neck dissection specimen will ordinarily include10 or more lymph nodes. Histological examination of a radical or modified radical neck dissection specimen will ordinarily include 15 or more lymph nodes.

pNX Regional lymph nodes cannot be assessed

pN0 No regional lymph node metastasis

pN1 Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension without extranodal extension

pN2 Metastasis described as:

pN2a Metastasis in a single ipsilateral lymph node, less than 3 cm in greatest dimension with an extranodal extension or, more than 3 cm but not more than 6 cm in greatest dimension without extranodal extension

pN2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, without extranodal extension

pN2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension, without extranodal extension

pN3a Metastasis in a lymph node more than 6 cm in greatest dimension without extranodal extension

pN3b Metastasis in a lymph node more than 3 cm in greatest dimension with an extranodal extension or, multiple ipsilateral, or any contralateral or bilateral node(s) with extranodal extension

Clinical stage group	T	N	M	Pathological stage group
0	T_{is}	N0	M0	0
I	T1	N0	M0	I
II	T2	N0	M0	II
III	T3	N0	M0	III
	T1-3	N1	M0	
IVA	T4a	N0-1	M0	IVA
	T1-4a	N2	M0	
IVB	T4b	Any N	M0	IVB
	Any T	N3	M0	
IVC	Any T	Any N	M1	IVC

Oropharynx p16 negative or p16 status unknown:

T staging

TX Primary tumour cannot be assessed

T0 No evidence of primary tumour

Tis Carcinoma in situ

T1 Tumour 2 cm or less in greatest dimension

T2 Tumour more than 2 cm but not more than 4 cm in greatest dimension

T3 Tumour more than 4 cm in greatest dimension or extension to lingual surface of epiglottis

T4a Tumour invades any of the following: larynx,* deep/extrinsic muscle of tongue(genioglossus, hyoglossus, palatoglossus, and styloglossus), medial pterygoid, hard palate, or mandible.

T4b Tumour invades any of the following: lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, skull base; or encases carotid artery

Note: * Mucosal extension to lingual surface of epiglottis from primary tumours of the base of the tongue and vallecula does not constitute an invasion of the larynx.

N staging

Nx Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension without extranodal extension

N2 Metastasis described as:

N2a Metastasis in a single ipsilateral lymph node more than 3 cm but not more than6 cm in greatest dimension without extranodal extension

N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, without extranodal extension

N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension, without extranodal extension

N3a Metastasis in a lymph node more than 6 cm in greatest dimension without extranodal extension

N3b Metastasis in a single or multiple lymph nodes with clinical extranodal extension*

Pathological Nodal staging

Oropharynx p 16 Negative

pNX Regional lymph nodes cannot be assessed

pN0 No regional lymph node metastasis

pN1 Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension without extranodal extension

pN2 Metastasis described as:

pN2a Metastasis in a single ipsilateral lymph node, less than 3 cm in greatest dimension with an extranodal extension or more than 3 cm but not more than 6 cm in greatest dimension without extranodal extension

pN2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in

greatest dimension, without extranodal extension

pN2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension, without extranodal extension

pN3a Metastasis in a lymph node more than 6 cm in greatest dimension without extranodal extension

pN3b Metastasis in a lymph node more than 3 cm in greatest dimension with an extranodal extension or, multiple ipsilateral, or any contralateral or bilateral node(s) with extranodal extension

Clinical stage group	T	N	M	Pathological stage group
0	T_{is}	N0	M0	0
I	T1	N0	M0	I
II	T2	N0	M0	II
III	T3	N0	M0	III
	T1-3	N1	M0	
IVA	T4a	N0-1	M0	IVA
	T1-4a	N2	M0	
IVB	T4b	Any N	M0	IVB
	Any T	N3	M0	
IVC	Any T	Any N	M1	IVC

Oropharynx – p16-Positive Tumours:

Tumours that have positive p16 immunohistochemistry overexpression.

T1 Tumour 2 cm or less in greatest dimension

T2 Tumour more than 2 cm but not more than 4 cm in greatest dimension

T3 Tumour more than 4 cm in greatest dimension or extension to lingual surface of epiglottis

T4 Tumour invades any of the following: larynx*, the deep/extrinsic muscle of tongue(genioglossus, hyoglossus, palatoglossus, and styloglossus), medial pterygoid, hard palate, mandible*, lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, skull base; or encases carotid artery

Note: * Mucosal extension to lingual surface of epiglottis from primary tumours of the base of the tongue and vallecula does not constitute an invasion of the larynx.

Oropharynx p-16 Positive

Clinical

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Unilateral metastasis, in lymph node(s), all 6 cm or less in greatest dimension

N2 Contralateral or bilateral metastasis in lymph node(s), all 6 cm or less in greatest dimension

N3 Metastasis in lymph node(s) greater than 6 cm in dimension

Clinical group staging

Clinical stage group	T	N	M
0	T_{is}	N0	M0
I	T1	N0/N1	M0
	T2	N0/N1	M0
II	T1-2	N2	M0
	T3	N0-2	M0
III	T1-3	N3	M0
	T4	Any N	M0
IV	Any T	Any N	M1

Pathological group staging

Pathological stage group	T	N	M
0	Tis	N0	M0
I	T1-2	N0-1	M0
II	T1-2	N2	M0
	T3	N0-1	M0
III	T3-4	N2	M0
IV	Any T	Any N	M1

Nasopharynx

T staging

T1 Tumour confined to the nasopharynx, or extends to the oropharynx and/or nasal cavity without parapharyngeal involvement

T2 Tumour with extension to parapharyngeal space and/or infiltration of the medial pterygoid, lateral pterygoid, and/or prevertebral muscles

T3 Tumour invades bony structures of skull base cervical vertebra, pterygoid structures, and/or paranasal sinuses

T4 Tumour with intracranial extension and/or involvement of cranial nerves,

hypopharynx, orbit, parotid gland and/or infiltration beyond the lateral surface of the lateral pterygoid muscle.

N staging

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Unilateral metastasis, in cervical lymph node(s), and/or unilateral or bilateral

metastasis in retropharyngeal lymph nodes, 6 cm or less in greatest dimension,

above the caudal border of the cricoid cartilage

N2 Bilateral metastasis in cervical lymph node(s), 6 cm or less in greatest dimension, above the caudal border of the cricoid cartilage

N3 Metastasis in cervical lymph node(s) greater than 6 cm in dimension and/or extension below the caudal border of the cricoid cartilage

Stage grouping:

Clinical stage group	T	N	M
0	T_{is}	N0	M0
I	T1	N0	M0
II	T1	N1	M0
	T2	N0/1	M0
III	T1-2	N2	M0
	T3	N0-2	M0
IVA	T4	N0-2	M0
IVB	Any T	N3	M0
IVC	Any T	Any N	M1

Kadish staging for esthesioneuroblastoma(34)

A- In situ or limited to the septum, floor, lateral wall, meatus, nasal concha, and vestibule with or without bony invasion

B- Origin in the paranasal sinuses or further extension into the paranasal sinuses and nasoethmoidal complex

C- Cases with extension into the skull base, palate, cribriform plate, medial wall or floor of the orbit, pterygoid plates, nasopharynx, skin, dura, and brain

D- With nodal disease or metastatic disease

TNM staging for Nasal cavity and paranasal sinuses

T – Primary Tumour

TX Primary tumour cannot be assessed

T0 No evidence of primary tumour

Tis Carcinoma in situ

Maxillary Sinus

T1 Tumour limited to the mucosa with no erosion or destruction of bone

T2 Tumour causing bone erosion or destruction, including extension into the hard palate and/or middle nasal meatus, except extension to posterior wall of maxillary sinus and pterygoid plates

T3 Tumour invades any of the following: bone of posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa, or ethmoid sinuses

T4a Tumour invades any of the following: anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinuses T4b Tumour invades any of the following: orbital apex, dura, brain, middle cranial fossa,

cranial nerves other than maxillary division of trigeminal nerve (V2), nasopharynx, or clivus

Nasal Cavity and Ethmoid Sinus

T1 Tumour restricted to one subsite of the nasal cavity or ethmoid sinus, with or without bony invasion

T2 Tumour involves two subsites in a single site or extends to involve an adjacent site within the nasoethmoidal complex, with or without bony invasion

T3 Tumour extends to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribriform plate

T4a Tumour invades any of the following: anterior orbital contents, the skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses

T4b Tumour invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than V2, nasopharynx, or clivus

N – Regional Lymph Nodes

N1 Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension without extranodal extension

N2 Metastasis described as:

N2a Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension without extranodal extension

N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, without extranodal extension

N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension, without extranodal extension

N3a Metastasis in a lymph node more than 6 cm in greatest dimension without extranodal extension

N3b Metastasis in a single or multiple lymph nodes with clinical extranodal extension*

M – Distant Metastasis

M0 No distant metastasis

M1 Distant metastasis

pTNM Pathological Classification

The pT categories correspond to the clinical T categories.

pN – Regional Lymph Nodes

Histological examination of a selective neck dissection specimen will ordinarily include10 or more lymph nodes. Histological examination of a radical or modified radical neck dissection specimen will ordinarily include 15 or more lymph nodes.

pNX Regional lymph nodes cannot be assessed

pN0 No regional lymph node metastasis

pN1 Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension without extranodal extension

pN2 Metastasis described as:

pN2a Metastasis in a single ipsilateral lymph node, less than 3 cm in greatest dimension with an extranodal extension or, more than 3 cm but not more than 6 cm in greatest dimension without extranodal extension

pN2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, without extranodal extension

pN2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension, without extranodal extension

pN3a Metastasis in a lymph node more than 6 cm in greatest dimension without extranodal extension

pN3b Metastasis in a lymph node more than 3 cm in greatest dimension with an extranodal extension or multiple ipsilateral, or any contralateral or bilateral node(s) with extranodal extension

Stage grouping is same as for Oropharynx p16 negative.

Prognosis

The different subsites in head and neck cancers have a different prognosis, and it also differs with stage, histology and anatomical location of the tumour. It is mostly the T

stage of the disease and the presence or absence of nodal metastasis which serve as important prognostic factors related to survival.

Advanced T stage is associated with worse local control and overall survival. Also, advanced N stage predicts the increased risk of distant metastasis and worse survival. Presence of distant metastasis (M1) at the time of presentation indicates a poor prognosis. The presences of bone erosion, cranial nerve palsy or lower nodal level are all poor prognostic factors. Histology wise, Non-keratinizing and undifferentiated carcinomas are more radiosensitive and have a better prognosis than keratinizing squamous cell carcinoma.

HPV positive oropharyngeal tumours have a better prognosis as compared to their negative counterparts. Hence there are a series of de-escalation trials which are ongoing. These trials are based on three main strategies (1) Exploring cetuximab as an alternative to cisplatin when given concurrently with radiation. (2)Reduction of radiation dose when given in combination with chemotherapy as primary treatment (guided by induction chemotherapy response) and (3) Reduction of adjuvant chemotherapy or radiotherapy dose following primary treatment with surgery (guided by histopathological features in the resected specimen).

Management overview of head and neck cancers

Generally, management for early stages I and II is single modality treatment with surgical resection and dissection of the draining lymph nodal groups or radical radiation therapy.

Stages III and locally advanced stage IV requires multimodality treatment including radical chemoradiation therapy or surgery followed by postoperative radiation therapy +/- chemotherapy.

Surgery

When different modalities are available, the modality that gives maximum chance of cure should be used. When different modalities have similar results, a modality that gives a better quality of life, with organ / function preservation is preferred.

Surgery is preferred over radiotherapy as a single modality in (1) sites where surgery is not morbid (cosmetically and functionally), (2) lesions involving or close to bone - to prevent radionecrosis, (3) young patients – possibility of a subsequent second primary and (4) presence of submucous fibrosis (SMF). Reconstruction options with good cosmesis should be planned prior to surgery.

Radiotherapy is preferred over surgery as a single modality, where (1) severe impairment of function / cosmesis with surgery, e.g. base tongue, glottis, (2) surgery is technically difficult with high morbidity and poor results e.g. nasopharyngeal carcinoma, (3) patient refuses surgery and (4) high risk of surgery.

Postoperative radiation therapy without chemotherapy

Indications:

Primary:

(1) Large primary – T3/T4

(2) Deep infiltrative tumour

(3) A high-grade tumour

(4) Lymphovascular and perineural invasion

(5) Level IV/ V nodes in the oral cavity and oropharyngeal tumours

Lymph nodes:

(1) Bulky nodal disease N2/N3

(2) Extranodal extension

(3) Multiple level involvement

(4) Multiple nodes

Postoperative chemoradiotherapy

Indications:

(1) Positive or close margin after curative resection

(2) Nodes with perinodal extension

Brachytherapy

Indications:

(1) Accessible lesions

(2) Small (preferable < 3 cm) tumours

(3) Lesions away from the bone

(4) N0 nodal status

(5) Superficial lesions

The dose for radical brachytherapy:

T1-2 N0: Radical Brachytherapy: 60-70Gy low dose rate Iridium (^{192}Ir) or 48Gy in 12 fractions (4 Gy twice daily) over 6 days with fractionated high dose rate.

T1-3 N0-1:

External RT 56 -60Gy in 28-30 fractions over 6wks followed by a boost with brachytherapy Low dose rate 192Iridium: 15-20 Gy or High Dose rate: 14Gy in 4 fractions over 2 days (4-3-3-4 Gy)

Organ preservation

"Organ preservation" means to maintain an organ in an unchanged condition or to avoid its loss, whereas "function preservation" means that the function is preserved whether the organ is totally or partially preserved. Traditionally the surgery for advanced laryngeal, oro-hypopharyngeal cancers was always mutilating with loss of function. Organ preservation involves the use of multimodality treatment including radiation therapy, chemotherapy, biologicals and function-preserving surgery to help maintain the functional status of the organ.

Chemotherapy

Chemotherapy has a role in concurrent, neoadjuvant setting in locally advanced tumours or as palliative chemotherapy in metastatic tumours.

Cisplatin is the drug of choice for use concurrently with radiation therapy. Trials with concurrent chemotherapy Cisplatin showed significant benefit in head and neck cancers. The MACH-NC meta-analysis showed the benefit of adding concurrent chemotherapy to radiation therapy in head and neck cancers and results showed an improvement in overall survival rates at 5 years with the addition of concurrent chemotherapy.

Neoadjuvant chemotherapy downsizes atumour that further helps in surgical resection with adequate margins or for better delivery of radiation therapy. The TAX 323 and 324 trials show that in locally advanced unresectable head and cancers, neoadjuvant chemotherapy with Docetaxel, Cisplatin and 5 Fluorouracil, had long-term survival benefit in patients with unresectable disease.

Biologic therapy

Squamous cell carcinomas of the head and neck that overexpresses EGFR tends to have poor prognosis. Cetuximab is a monoclonal antibody that selectively targets EGFR receptor.Boner et al have shown that concurrent cetuximab with radical radiation therapy for locally advanced head and neck cancer improves locoregional control and reduces mortality without increasing common toxic side effects. Concurrent cetuximab is used for patients who cannot tolerate concurrent chemotherapy in view of poor performance status.

Nimotuzumab is another anti-EGFR monoclonal antibody, which has been proven to be safe to use concurrently with radiation therapy. Tyrosine kinase inhibitors like Gefitinib and Erlotinib can be used in the palliative setting for metastatic tumours.

Adverse effects of treatment

With advances in radiation therapy technology and multimodality treatment methods by addition of concurrent chemotherapy, multiple trials showed improvement in survival of patients with advanced head and neck cancer. The adverse effects of treatment would be of much significance in patients with increased survival and longer follow up.

The common side effects that were observed with head and neck radiation therapy included:

a. Xerostomia
b. Mucositis
c. Candidiasis
d. Dysguesia
e. Dental caries
f. Osteoradionecrosis
g. Trismus
h. Oral Pain
i. Dermatitis, soft tissue fibrosis
j. Dysphagia
k. Dysphonia

Radiation therapy techniques

Conventional RT

In conventional radiation therapy, patients were planned with 2-dimensional conventional methods of planning in which X-rays were taken to define the field borders. The field borders are placed depending on the anatomical extent of a tumour and the nodal spread of the disease. In the conventional planning methods, it is difficult to reduce the dose to the adjacent normal structures, without compromising the dose to the primary tumour. The radiation therapy beams deliver the same dose throughout to the primary tumour and to the adjacent normal structures. Customized blocks may be used to decrease the radiation dose to the normal tissue. However, the process of making customized blocks is very cumbersome and even with their use; the normal tissue still receives a very high dose. Thus, the therapeutic index for such a planning technique is very small with very high rates of complications due to increased radiation dose to normal tissue.

Conformal RT

It was the use of CT in radiation planning that led to innovations in planning techniques which included contouring of the tumour and the normal structures in each of the CT axial slices and delivering radiation more conformally to the tumour and areas at risk by avoiding the organs at risk. This was made possible by shaping the radiation beam with the use of multileaf collimators (MLCs). This comprised the 3dimensional conformal radiation therapy or 3DCRT.

Even though in 1982, the concept of modulating the intensity of radiation beam was proposed by Brahme, it was not until the early years of the 21st century that this came into clinical practice as Intensity-modulated radiation therapy or IMRT.

About Intensity modulated radiation Therapy (IMRT)

IMRT is an advanced form of three-dimensional conformal radiotherapy. The introduction of CT into radiation oncology in the 1980s enabled treatment planning based on three-dimensional anatomical information of the tumour and surrounding healthy tissues, thus facilitating the establishment of three-dimensional conformal radiotherapy (3D-CRT). The key features of 3D-CRT treatment planning include beam's eye view (BEV) design of treatment fields and plan evaluation. BEV allowed for finding a beam direction that could irradiate the tumour without the beam passing through nearby critical organs. Dose-volume histograms (DVHs) and isodose distributions became essential tools for plan evaluation. Together with the progress in 3D image processing, the 3D volume information from CT also enabled accurate dose calculation using the convolution-superposition method, allowing the inhomogeneous distribution of tissues to be more accurately handled. (36)

Whereas 3D-CRT exploits field shape conformation to improve target dose conformality, the organs at risk (OARs) located in the groove region of concave target volumes cannot be saved from the target dose.

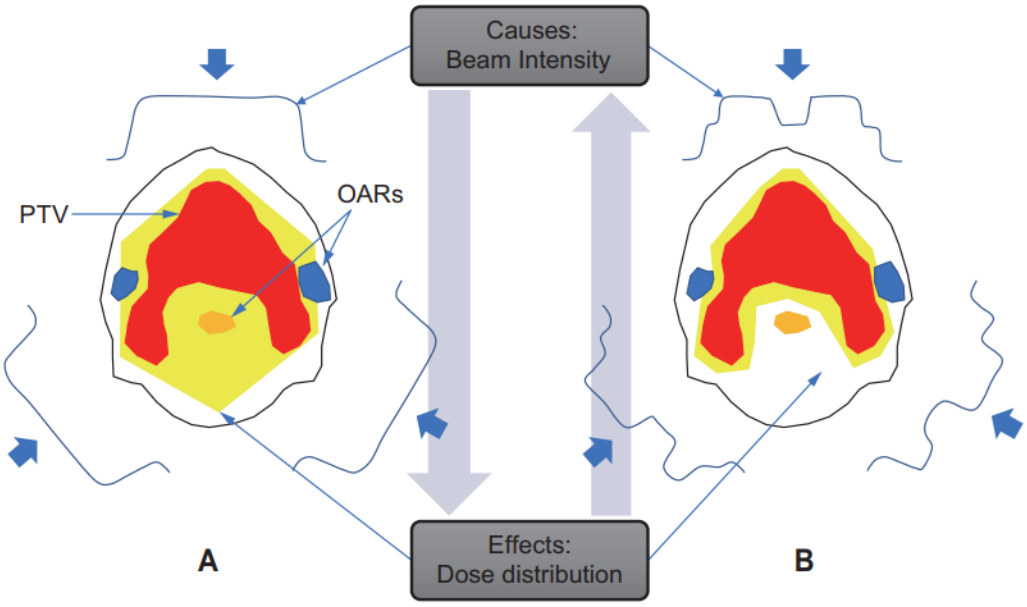


Fig (iv) *Comparison of the principle of 3D-CRT (A) and IMRT (B) with illustrations of forward vs. inverse planning. Considering the dose calculation problem of radiation therapy in terms of the concept of causality, while the causes are beam parameters including energy, direction, size, and intensities, the effects are dose distributions.*

In conventional 3D-CRT, the irradiation field shape coincides with the shape of the target according to the incidence direction of the irradiation beam, while in IMRT, the beam intensity is modulated according to the arrangement of the target and surrounding organs. The intensities of the rays that pass through OARs are reduced, while the intensities of the rays go primarily through the target volume are increased. The inhomogeneity caused by the 'intentionally non-uniform intensity' of a beam is compensated for by beams from other directions. Physically, a feature of the IMRT technique is to enhance control over the 3D dose distribution through the superposition of a large number of independent segmented fields, either from a

number of fixed directions or from directions distributed on one or more arcs. By this method of adding intensity modulation to geometric shaping, the IMRT dose distribution can be rendered concave, as opposed to the convex-shaped coverage accomplished with 3D-CRT, where geometric conformal shaping of a uniform intensity beam is performed. Therefore, IMRT can enable dose reduction to OARs located within a concave area of the planning target volume (PTV).

It is of particular value for target volumes with concave or complex shapes with close proximity to radiosensitive normal structures. It has two key additional features compared to conformal radiotherapy: (a) non-uniform intensity of the radiation beams and (b) computerized inverse planning(37). The major salivary glands(38), the mucosa of the pharynx or of the oral cavity, the larynx(39), the constrictor muscles(40), the mandible(41), and the inner and middle ears(42) are examples of structures that can be partially spared when clinically feasible, due to the dose conformality afforded by IMRT.

DVH and Dose-volume metrics

A histogram may be plotted according to the usual mathematical definition, as the accumulated volume of those elements receiving a dose in a specified dose interval against a set of equispaced dose intervals. This is referred to as a differential dose-volume histogram.

A more useful technique is to, however, plot the data as the volume receiving a dose greater than or equal to a given dose against that dose over the expected dose range. These plots are actually cumulative dose-volume frequency distributions. These

cumulative DVHs are more commonly used for plan evaluation. The lack of spatial information is a major limitation of DVHs.

The data from DVH can be expressed in terms of dose received to a defined volume of the structure, or as a percentage of volume receiving a defined dose.

ADVH metric is a character string which has *three mandatory elements* in the following order:

* 1st letter is either "D" or "V": "D" if the requested value is a dose, "V" if it is a volume.

* 2nd element (number): If the first letter is "D", this gives the volume for which the dose value of the cumulative DVH should be reported. If the first letter is "V", this gives the dose for which the volume value of the cumulative DVH should be reported.

* 3rd element (measurement unit): The measurement unit for the 2nd element of the metric. Absolute volumes are indicated by "CC" for cm3, relative volumes by "%".

Absolute doses are indicated by "Gy" for Gray or "cGy" for centigray, relative doses by "%".

For Example:

$D_{33\%}$: Dose received by 33% of the volume of the defined structure

D_{2cc}: Dose received by 2cc of the volume of the defined structure

V_{45Gy}: Volume of the defined structure which receives at least 45Gy.

Larynx as an OAR and Constraints in literature for larynx

Voice is important in speech and communication for two reasons: (1) Vocal delivery can help us engage and interest the audience. (2) Vocal delivery helps ensure that our ideas are communicated clearly. The different components of speech delivery are the rate, volume, pitch, articulation, pronunciation, and fluency.

The vocal cords are the structures in larynx or glottis which are responsible for voice production. Oedema to the vocal cords during radiation therapy and later can have an impact on the quality of the voice, and in future can cause social handicap. This explains the relevance that the larynx has as an important organ at risk during the radiation therapy of head and neck cancers.

Organs at risk or critical normal structures are tissues that if irradiated could suffer significant morbidity and thus influence the treatment planning and the dose prescription. From multiple clinical studies, the critical doses at which significant damage that can occur to an OAR can be deduced. Care can be taken not to cross these dose and volume constraints during radiation planning in order to maintain an acceptable quality of life for the patient. Conformal radiation therapy with IMRT helps to further reduce the dose to these organs at risk.

The dose constraints for larynx used in RTOG 0922 was to keep the Mean Dose< 40 Gy or as low as possible. To reduce the incidence of severe laryngeal oedema, D_{mean} should be less than 43.5 Gy(39). Equivalent uniform dose to larynx should be less than 30 to 35 Gy(43) for grade 2 laryngeal oedema. When D_{mean} was less than 20 Gy, only 25% of patients had worse voice quality 6 months after radiation therapy(44).

Larynx contouring

There are three methods available in the literature for contouring of laryngeal structures. While two of them describes contouring larynx entirely as a single structure, the third describes steps for contouring sub-site-wise and cartilages separately.

1. Freedman et al

2. A standardized method for laryngeal contouring by Choi et al

3. DAHANCA, EORTC, GORTEC, HKNPCSG, NCIC CTG, NCRI, NRG Oncology and TROG consensus guidelines

1. Guide for contouring larynx by Freedman published in *Practical Radiation Oncology*(45)

This describes step by step guideline for contouring larynx based on the method used in RTOG 1016 trial.

Step one: Identify the most inferior edge of the hyoid bone and begin contouring on the next slice inferiorly.

Step two: The anterior boundary of the larynx contour is the inner surface of the thyroid cartilage. In the superior portion of the contour, the posterior boundary of the larynx is the lateral surfaces of the aryepiglottic folds and the posterior surface of the mucosa covering the arytenoids. Do not include the pyriform sinus in the larynx

contour. In the inferior portion of the contour, the posterior boundary of the larynx is the posterior surface of the cricoid cartilage.

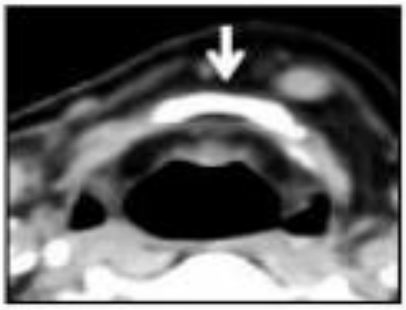
Step three: The most inferior extent of the larynx contour is the last image where the cricoid cartilage is seen as a complete ring.

2. **The standardized method by Choi published in *Radiation Oncology*(46)**

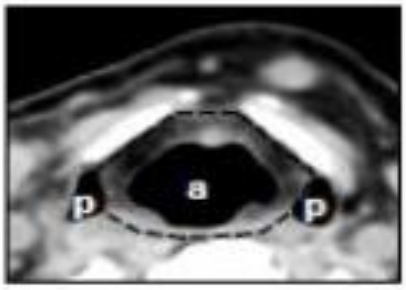
The thyroid, arytenoid and cricoid cartilages are contoured first. The aryepiglottic folds and false cords are contoured as a single structure as they are difficult to be identified separately by imaging, than by direct visualization.

The epiglottis is contoured separately as suprahyoid part and infrahyoid part and combined together to form Epiglottis. Epiglottis, arytenoids, and the anteromedial wall of the aryepiglottic folds and false vocal folds are combined together to form the Supraglottis OAR. The postero-lateral wall of the aryepiglottic folds forms the medial wall of the pyriform sinuses and is part of the hypopharynx.

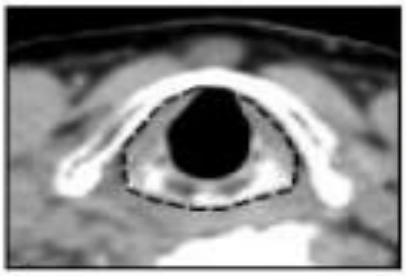
The larynx OAR is created by combining the supraglottic larynx, glottic larynx, subglottic larynx, thyroid cartilage, and cricoid cartilage contours.



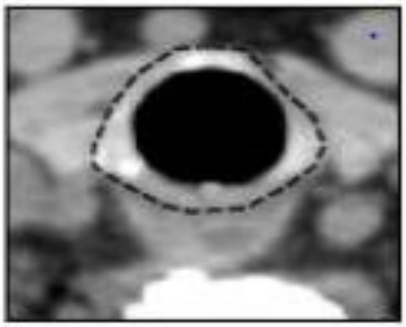
Most inferior edge of hyoid bone (arrow).
Do not contour the larynx at this level



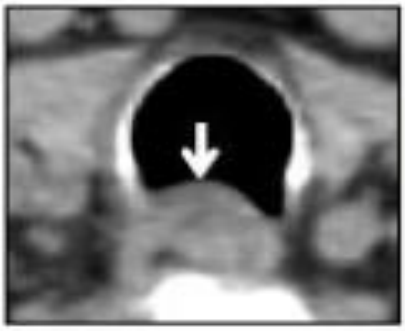
Most Superior Larynx Contour:
On the first image where you do not see the hyoid bone as you go inferiorly.



The boundary of the larynx contour is the inner edge of the thyroid cartilage anteriorly and the posterior edge of the cricoid cartilage posteriorly.



Most Inferior Larynx Contour:
The last image where you see the cricoid cartilage as a complete ring. The larynx contour is the outer surface of the cricoid cartilage



The larynx contour is not present on images where the posterior wall of the airway has a convex or membranous appearance (arrow).

Fig (v): *Landmarks for Contouring of larynx as per Freedman et al. Do not include pyriform sinus and air in the laryngeal contour*.

3. DAHANCA, EORTC, GORTEC, HKNPCSG, NCIC CTG, NCRI, NRG Oncology and TROG consensus guidelines(47)

EORTC describes contouring of larynx separately as Supraglottic larynx, glottic area and arytenoids.

The supraglottic larynx is delineated according to Christiansen et al. (48). Anatomic borders are as listed below:

Cranial: Tip of the epiglottis

Caudal: the Cranial edge of arytenoid cartilages

Anterior: Hyoid bone, pre-epiglottic space, thyroid cartilage

Posterior: Inferior PCM, pharyngeal lumen

Lateral: Thyroid cartilage

Medial: Pharyngeal lumen

The glottic area is contoured as including the vocal cords and paraglottic fat. Air should be excluded from the contour. Borders are as below:

Cranial: the cranial edge of arytenoid cartilages

Caudal: the Caudal edge of anterior part of the thyroid cartilage.

Posterior: Cricoid, anterior border arytenoids.

The arytenoids (or arytenoids cartilage) is defined as a separate structure. The base (caudal edge) of each arytenoid is broad for articulation with the cricoid cartilage. The apex (cranial edge) is pointed.

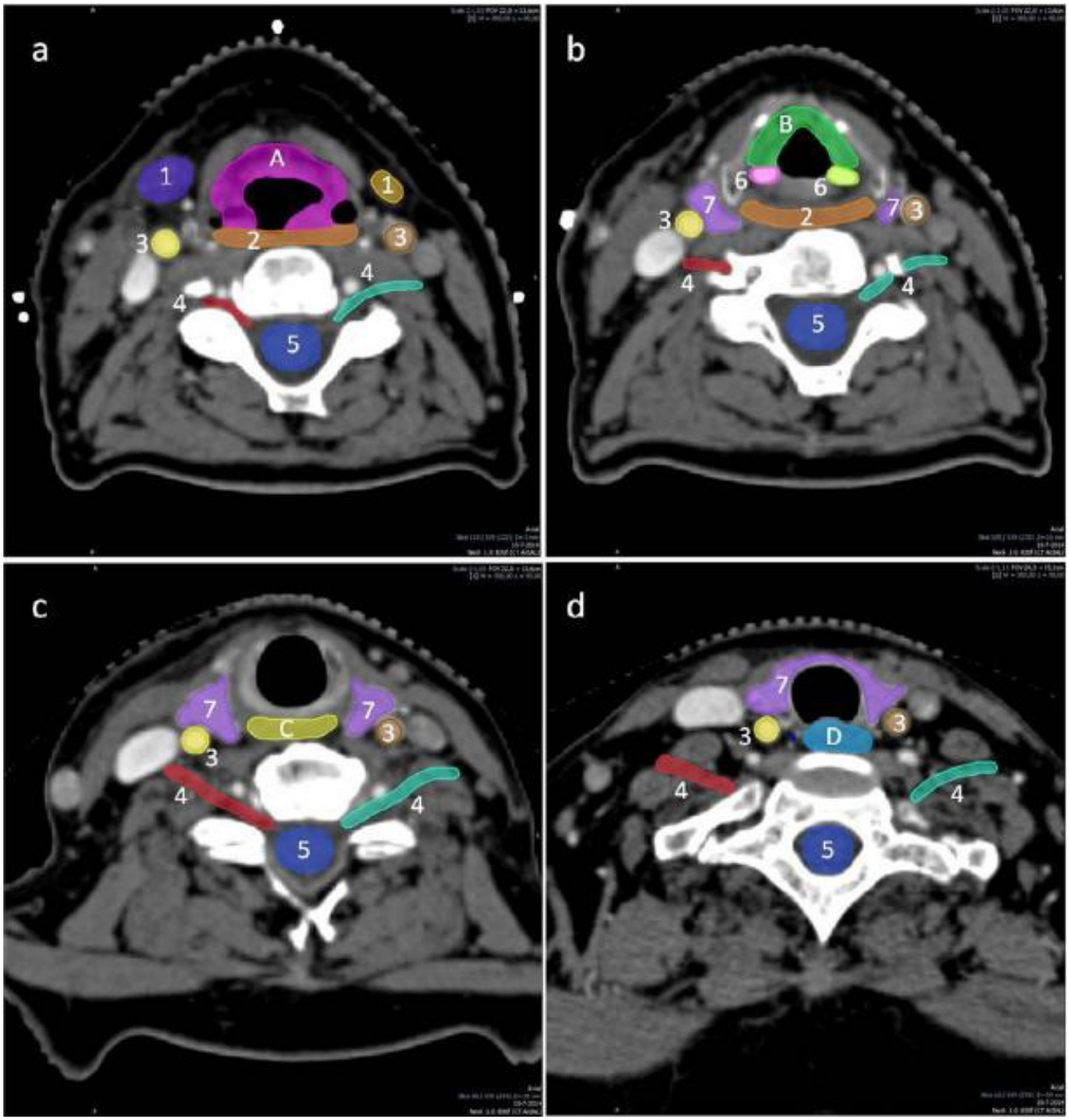


Figure (vi): Axial CT slices of neck region: *Showing delineation of the supraglottic larynx (A) glottic area (B) cricopharyngeal inlet muscle (C) and cervical oesophagus (D). Other organs at risks visible are the submandibular glands (1), pharyngeal constrictor muscles (2), carotid arteries (3), brachial plexus (4), spinal cord (5), arytenoids (6) and thyroid (7).*

Grading systems for laryngeal oedema

Radiation therapy induced laryngeal oedema is common and expected side effect. The grade of larynx oedema can be scored as per the RTOG scale, CTCAE v5.0 and Chandler's classification.

RTOG grading of Laryngeal oedema(49)

RTOG grading is as follows: 0, no edema; 1, slight edema; 2, moderate edema; 3, severe edema; and 4, necrosis. The grade 1 and 2 oedema is defined as "slight" and "moderate" oedema, which poses a certain amount of uncertainty. Grade 1 oedema corresponds to minimal thickening of the epiglottis, aryepiglottic folds, arytenoids and false cords. Grade 2 is a more diffuse and evident oedema, although still without significant to symptomatic airway obstruction. Grade 3 is oedema causing airway compromise and grade 4 is with necrosis.

CT-CAE v5.0 grading of Laryngeal oedema(50)

1- Asymptomatic; clinical or diagnostic observations only; intervention not indicated

2- Symptomatic; medical intervention indicated (e.g., dexamethasone, epinephrine, antihistamines)

3- Stridor; respiratory distress; hospitalization indicated

4- Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)

5- Death

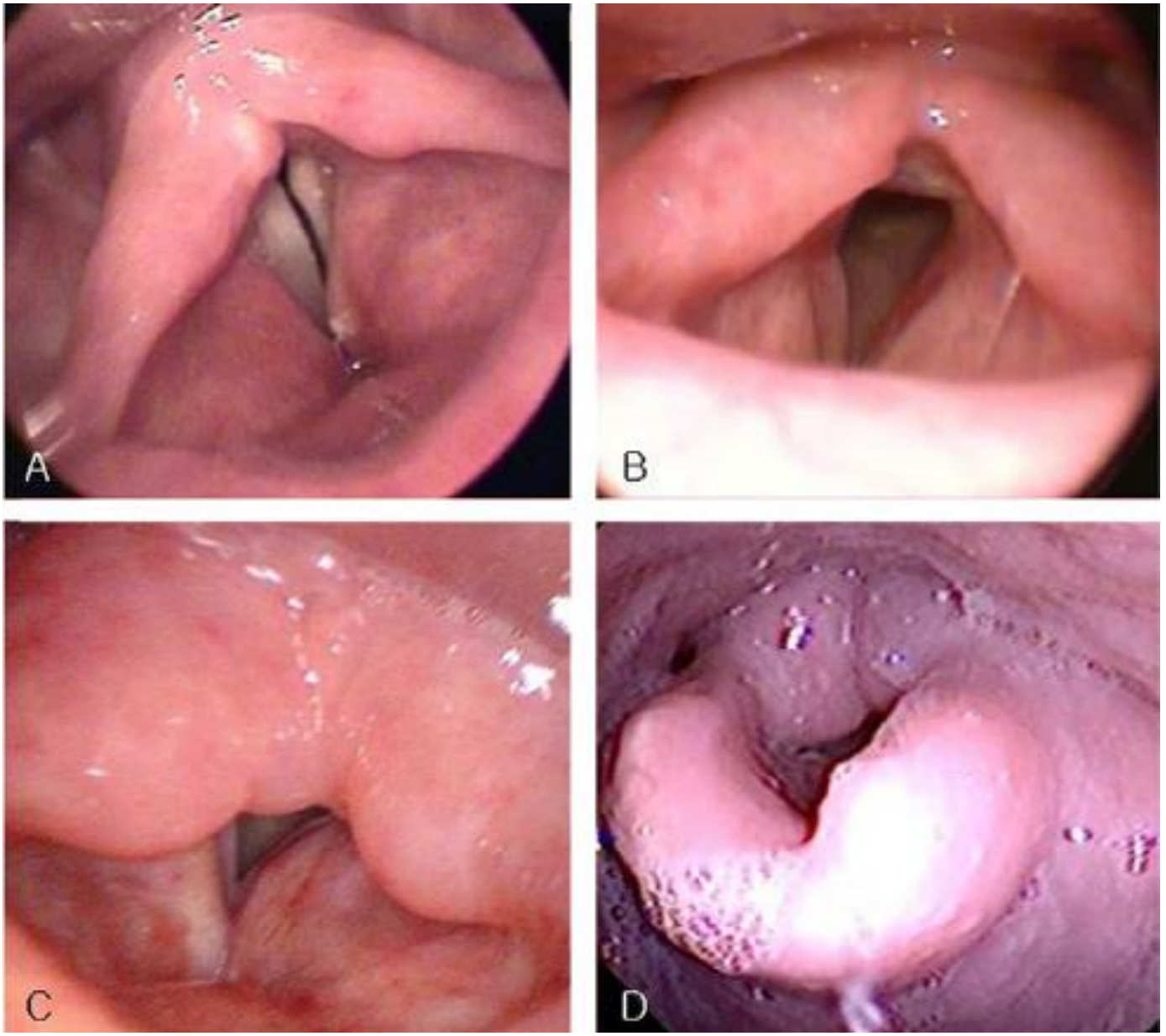


Fig (vii): Laryngoscopic view showing laryngeal oedema grades as per RTOG grading. Grades 0 (A, normal), 1 (B, mild), 2 (C, moderate), and 3 (D, severe) on RTOG classification.

Chandler's Classification (49)

Grade 1:

Symptoms may include: Slight hoarseness and mucosal dryness

Signs may include: Slight oedema and presence of telangiectasias.

Grade 2:

Symptoms may include: Moderate hoarseness and mucosal dryness.

Signs may include: Moderate oedema and erythema, some TVC, hypomobility

Grade 3:

Symptoms may include: Severe hoarseness with dyspnea, moderate odynophagia and dysphagia

Signs may include: Marked oedema, skin changes anterior neck, severely impaired or fixed unilateral TVC

Grade 4:

Symptoms may include: Respiratory distress, severe pain and odynophagia, weight loss, dehydration

Signs may include Fistula, fetid odour, fever, severe skin changes anterior neck and laryngeal airway obstruction due to oedema.

Methods of assessing laryngeal toxicity in RT

Objective methods

The vocal function can be assessed quantitatively by three methods:

(i) Videostroboscopy(51) for direct visualization to assess the supraglottic activity, vocal fold edge, amplitude, mucosal wave, phase asymmetry and glottis closure.

(ii) Aerodynamic measurements of phonation time and

(iii) Direct human observation by Direct laryngoscopy(52).

(i) Videostroboscopy

Laryngeal videostroboscopy (LVS) is the gold standard for evaluation of dysphonia and laryngeal function (53). LVS is an endoscopic tool that uses synchronized pulsed light at a frequency allowing the examiner to observe normal and pathologic vocal fold (VF) vibration and movement during phonation. A Strobe light is a flashing light that enables us to see a simulated picture of vocal fold vibrations in slow motion

Stroboscopy is a special method, done as an office procedure, and is used to visualize vocal fold vibration by recording the video of the vocal cords while patient phonates. It uses a synchronized, flashing light passed through a flexible or rigid telescope. The flashes of light from the stroboscope are synchronized to the vocal fold vibration at a slightly slower speed, allowing the examiner to observe vocal fold vibration during sound production in what appears to be slow motion. The video which appears as in a

slower speed is actually an illusion because the speed of the vocal cord vibration is not changed by stroboscopy.

Within the oncologic realm, LVS has most commonly been used for the diagnosis of early-stage glottic cancers but has also been employed as a metric of posttreatment voice. LVS offers improved diagnostic sensitivity over non-stroboscopic video laryngoscopy as it permits evaluation of functional changes in VF biomechanics and vibration. LVS can be used in tandem with validated perceptual voice assessments in order to correlate dysphonia with specific physiologic findings. To date, there is limited experience using LVS to assess the impact of definitive RT upon functional voice outcomes. (54) Marciscano et al(55) has used videostroboscopy for assessment of voice quality in patients with early glottic cancers post radiotherapy on follow up.

Fig (viii) A rigid video stroboscope

(ix) Flexible videostroboscopy being performed on a patient

(ii) Aerodynamic measurements

Abnormal acoustic and aerodynamic measures are attributed to impairment of vocal fold vibration, as observed stroboscopically, with incomplete closure and reduced mucosal wave, as well as observed ventricular activity, the latter indicative of hyperfunction. (56)

Electroglottographic (EGG) analyses of voice have revealed superior voice outcomes after primary chemoradiotherapy compared with patients with total laryngectomy and transesophageal puncture (TEP), with improvement over a 12-month period in the

chemoradiotherapy group (57). In postradiotherapy nasopharyngeal cancer patients, EGG analysis of vocal fold vibratory behaviour revealed higher speech quotient, a ratio of glottic opening time to closing time, and lower open quotient, an indication of longer closed phase relative to open phase in the cycle in these patients as compared with healthy controls. Both of these measures reflect increased vocal tension or resistance. These authors also found lower signal-to-noise ratios, indicative of voice abnormality. Others have found abnormal perturbation scores and abnormal perceptual ratings in patients treated with radio/chemoradiotherapy to the larynx. Abnormal measures of jitter, shimmer, harmonics-to-noise ratio, and fundamental frequency (i.e., increase in fundamental frequency) have been seen in irradiated laryngeal cancer patients as well (58).

(iii) Direct Laryngoscopy(59)

Laryngoscopy can be performed either indirectly by an indirect laryngoscope or directly by an angled telescope or with fibreoptic laryngoscopy.

The traditional indirect laryngoscopy relies on a single hand-held mirror to reflect the structures of the larynx to sight.

Laryngoscopy by angled telescope allows a direct view of these structures also. Though both these techniques may be less expensive and easier to use initially, fiberoptic nasopharyngoscopy provides clearer visualization and better access to nasopharyngeal anatomy.

Fibre-optic flexible laryngoscope was initially developed in the 1930s by a medical student named Heinrich Lamm, followed by further innovations from Hopkins and Storz. It was in 1963, that a medically functional fiberoptic scope with higher resolution, lighting, suction, and instrument ports was designed by Hirschowitz. Current fiberoptic nasopharyngoscopes are lighted, are flexible with 2-way articulation, provide inline viewing with photo and video capabilities, and can have a distal diameter as small as 2 mm.

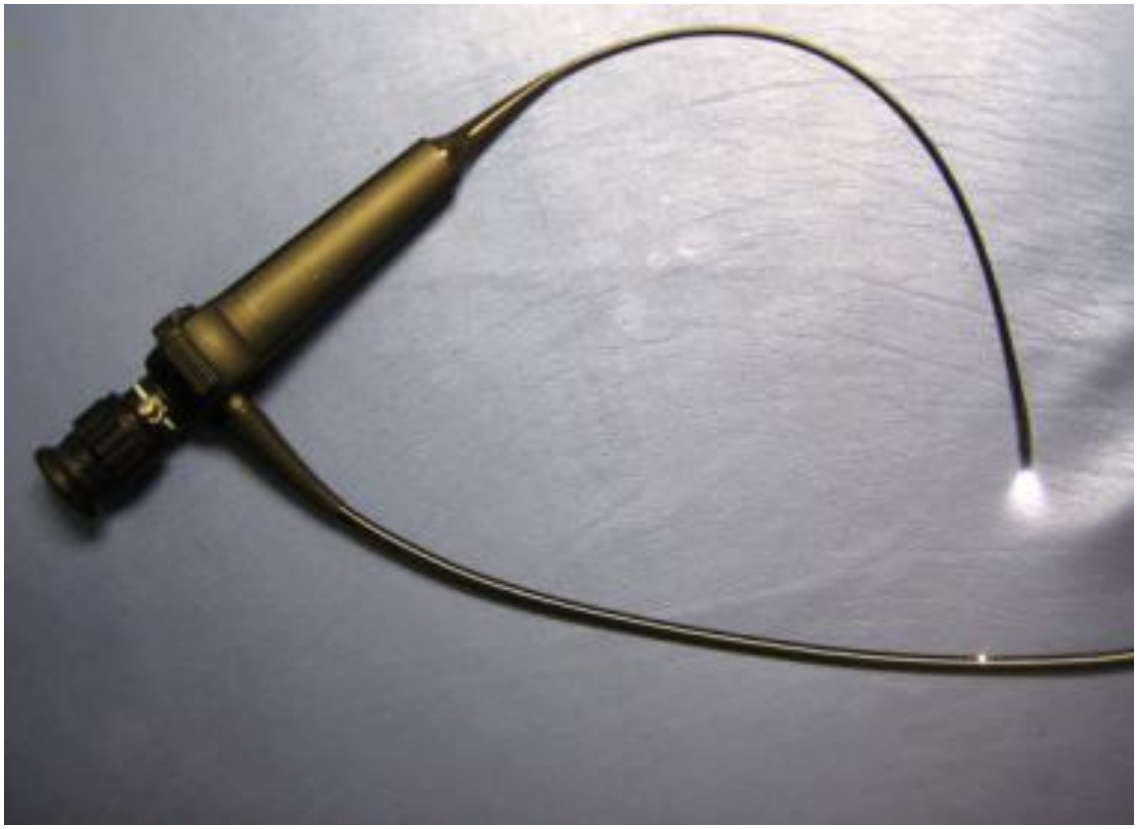


Fig (x): Flexible laryngoscope

Subjective methods

Voice problems after radiotherapy may be attributed to observable dryness of the laryngeal mucosa, muscle atrophy, fibrosis, hyperaemia, and erythema. There are

various validated questionnaires(60,61) which are available for subjective assessment of the voice and speech related quality of life.

(i)EORTC QLQC30/H&N35

EORTC designed a modular instrument designed to bridge the roles of disease-specific and global QOL scales. EORTC-QLQ-C30 was the core questionnaire (version 3.0). This consisted of 30 questions which were organized into 5 subdomains: physical (5), role (2), cognitive (2), emotional (4), and social (2). The global QOL assessment was done with H&N-35, which had 35 questions arranged into 7 domains.

(ii)The Functional Assessment of Cancer Therapy-Head and Neck (FACT-H&N)

FACT-G is a self-administered questionnaire which consists of 27 questions in 4 domains - physical (7), social/family (7), emotional (6), and functional (7). The 38 item FACT-H&N also includes an 11-item head and neck cancer specific subscale.

(iii) The Head and Neck Radiotherapy Questionnaire (HNRQ)

This is a questionnaire developed for use in patients with advanced stage (III and IV) malignancies to measure the radiation-induced acute morbidity and quality-of-life. It is a 22-item interviewer-administered scale representing 6 dimensions (skin, throat, oral stomatitis, digestion, energy, psychosocial), with each item rated on a 7-point Likert scale and 3 to 4 items per dimension. Higher scores were indicative of better quality of life.

(iv) Quality of Life Instrument for Head and Neck Cancer (QL-H&N)

This questionnaire focusses on the psychological factors and is quite short and sensitive with disease-specific questions. This is a self-administered questionnaire which consists of composite psychometric scales, with added disease-specific questions. The full questionnaire has not been published but is known to include 29 items. The physical, social and psychological domains are scored individually, but there is no summary score.

(v) Quality of Life Questionnaire for Advanced Head and Neck Cancer (QLQ)

The QLQ was designed and used in a UK study to discriminate between patients with advanced head and neck cancer randomized to either radiation alone or surgery and radiation. It was piloted as a 19-item self-assessed questionnaire, with 15 questions rated on a 4-point Likert type scale, and 4 questions rated on a 5-point scale. Details of scoring and the handling of missing responses have not been published.

(vi) Quality of Life - Radiation Therapy Instrument Head & Neck Module (QOL-RTI/H&N)

This was developed at the University of South Florida. The current QOL-RTI/H&N is a questionnaire with 39 items, self-administered. All questions use a 10-item Likert response scale. The general portion consists of 4 domains: functional (9 questions), emotional (7 questions), family and socioeconomic (6 questions) and general (3 questions). The disease-specific module has 14 items. The QOL-RTI and Head and Neck module are scored separately.

(vii) The University of Michigan Head and Neck Quality of Life (HNQOL)

This 21-item instrument was intended for the overall assessment of outcome for patients with head and neck cancer. It is an interviewer-administered questionnaire assessing four domains: pain (4), emotion (6), communication (4) and eating (6). Each item is rated on a 5-point Likert scale, and each domain generates a score of 0–100, with higher scores reflecting better QOL. In addition, a single item assesses "overall disturbance or bother" as a result of head and neck cancer. A summary score is not calculated.

(viii) University of Washington Quality of life questionnaire (UW QOL)

It is a self-administered instrument consisting of 12 questions: 9 disease-specific items (pain, chewing, swallowing, speech, shoulder disability, appearance, activity, recreation and employment), plus 3 general items measuring global health-related QOL, change in health-related QOL since diagnosis, and overall QOL. Each question has 3–6 response options, using a Likert-type scale. Each item is scored from 0–100, with higher scores indicating better QOL, resulting in a summary score of 0–900 for the disease-specific items. The general items are scored individually.

The UW QOL is a short instrument best suited to patients undergoing surgery. Although a recent revision has added some issues of potential importance to radiotherapy patients (dry mouth, change in taste), it is probably not the questionnaire of choice for patients undergoing radiation therapy.

Table (I) Comparing the Questionnaires of Disease-Specific Quality Of Life in Head and Neck Cancer

Table 2. Summary of disease-specific QOL instruments for head and neck cancer.

Criteria	EORTC	FACT	HNRQ	QL-H&N	QLQ	QL-RTI/HN	HNQOL	UWQOL
Purpose*	D,E	D,E	E	?	E	E	D,E	D
Target phase of illness†	A,C	A,C	A	?	A,C	A,C	A,C	A,C
Number of items	65	27	22	29	19	39	21	12
Summary score	No	Yes	Yes	No	?	Yes	No	Yes
Self-administered‡	+	+	–	+	+	+	–	+
Patient item generation‡	–	+	–	+	–	–	+	?
Patient item reduction‡	+	+	–	–	+	–	+/–	?
Internal reliability‡	+	+	+	+/–	–	+	+	–
Test-retest reliability‡	–	–	–	+/–	–	+	+	+/–
Face validity‡	+	+	+/–	?	+/–	?	+/–	?
Content validity‡	+	+	+/–	+/–	+	+	+/–	+/–
Concurrent validity‡	–	+	+/–	+/–	+/–	+/–	+/–	+
Responsiveness‡	+	+/–	+	–	–	–	–	+/–
Cross-cultural input‡	+	+/–	–	–	–	+/–	–	–

**D = discriminative; E = evaluative.*

†A = acute; C = chronic.

‡+ means criteria is present or has been demonstrated, – means it is absent or has not yet been demonstrated, +/– means limited or partial demonstration, and ? means the criteria cannot be assessed.

(ix)VOICE HANDICAP INDEX (VHI)

The VHI was developed using a sample of patients from diverse clinical settings with voice disorders thus encompassing a broad range of pathologies. There are a total of 85 items and they are grouped into three: functional (25 items), emotional (31 items), and physical (29 items). It was ensured that this scale had both content and face validity.

Construct validity was not fully evaluated in this study, although the relationship between patient self-perceived severity and VHI scores was determined to be moderately strong. There are no comparable scales to cross-validate construct validity for the VHI.

(x) VOICE RELATED QUALITY OF LIFE QUESTIONNAIRE (V-RQOL)

The V-RQOL questionnaire was developed by Hogikyan and Sethuraman(62) at the University of Michigan. V-RQOL is a self-administered questionnaire that measures the subjective burden due to a voice disorder. It is short and has only 10 items with 2 subscales: physical and social-emotional scales having 6 and 4 questions respectively. The overall V-RQOL score is assessed by the total scale.

The ten questions are as follows:

1. I have trouble speaking loudly or being heard in noisy situations.

2. I run out of air and need to take frequent breaths while talking

3. I sometimes do not know what will come out when I begin speaking

4. I am sometimes anxious or frustrated because of my

5. I sometimes get depressed because of my voice

6. I have trouble using the telephone (because of my voice)

7. I have trouble doing my job or practising my profession (because of my voice)

8. I avoid going out usually (because of my voice)

9. I have to repeat myself to be understood

10. I have become less outgoing (because of my voice)

Of the above questions, Numbers 4, 5, 8 and 10 are to assess the socioemotional quality of life; and the rest six of them belong to the physical domain. Each question has a 5 point Likert scale. The scoring is done by first adding all the points together for total; and the scores of only the corresponding questions for the socioemotional and physical domains. The formula for calculating the V-RQOL score is as follows:

Socioemotional V-RQOL score= $100-\left\{\left[\frac{Raw\ score-4}{16}\right]100\right\}$

Physical V-RQOL score= $100-\left\{\left[\frac{Raw\ score-6}{24}\right]100\right\}$

Total V-RQOL score= $100-\left\{\left[\frac{Raw\ score-10}{40}\right]100\right\}$

The detailed questionnaire and the method of scoring are attached in Appendix (III) and (IV).

The V-RQOL questionnaire has been validated in India in a study conducted in Tata Memorial Hospital, Mumbai, in two regional languages of Hindi and Marathi. In this study by Deshpande et al (63), V-RQOL scores were higher in patients younger than 50 years. Most of the patients (91%) received radiotherapy either preoperatively or postoperatively. Therefore the effect of radiotherapy on V-RQOL was not tested, though radiotherapy had shown a significant difference in other studies.

There was no statistically significant difference in V-RQOL whether surgery was done per upfront or as salvage after failure of radiotherapy. Sex, site of a tumour, type of surgery (including the extent of resection, type of closure, neurectomy, and myotomy) did not have any effect on the V-RQOL scores.

Correlation of DVH parameters with laryngeal oedema

Sanguineti et al(39) conducted a retrospective study in 66 patients with head and neck squamous cell carcinomas with uninvolved larynx who had undergone IMRT and had at least 1 fibreoptic laryngoscopy at 2 years of follow up. The dose volume parameters Dmean and V20 to V70 was evaluated from each plan. V_{30} to V70 showed correlation with Grade ≥2 oedema. The D_{mean} when kept below 43.5 Gy, there was no grade 2 oedema. By multivariate analysis, the predictors of laryngeal oedema were mean larynx dose and N+ stage.

Rancati et al(64) performed a study on 48 patients with head and neck non-laryngeal carcinomas for finding the best-fit parameters of normal tissue complication probability (NTCP) models for laryngeal oedema after radiotherapy for head and neck cancer. Flexible laryngoscopy was performed at 15 months for assessing laryngeal oedema. Patients who underwent any major surgery other than tonsillectomy and neck dissection was excluded. All patients underwent either IMRT or 3DCRT. 2 NTCP models were used- Lyman model and Logit model. In the Lyman model, DVH was reduced to the effective volume by Kutcher-Burman method (LKB). In the Logit model, DVH was reduced to Equivalent Uniform Dose (EUD) (LOGEUD). 25 out of 48 (52.1%) experienced G2–G3 oedema.

This was conducted in the same patient population as that of Sanguineti et al (39) and showed a large volume effect for laryngeal oedema. This is consistent with the parallel architecture of the larynx for this endpoint. An EUD of < 35 to 40 Gy was expected to reduce the risk of laryngeal oedema > grade 2 and this should be the dose objective for EUD based optimization IMRT.

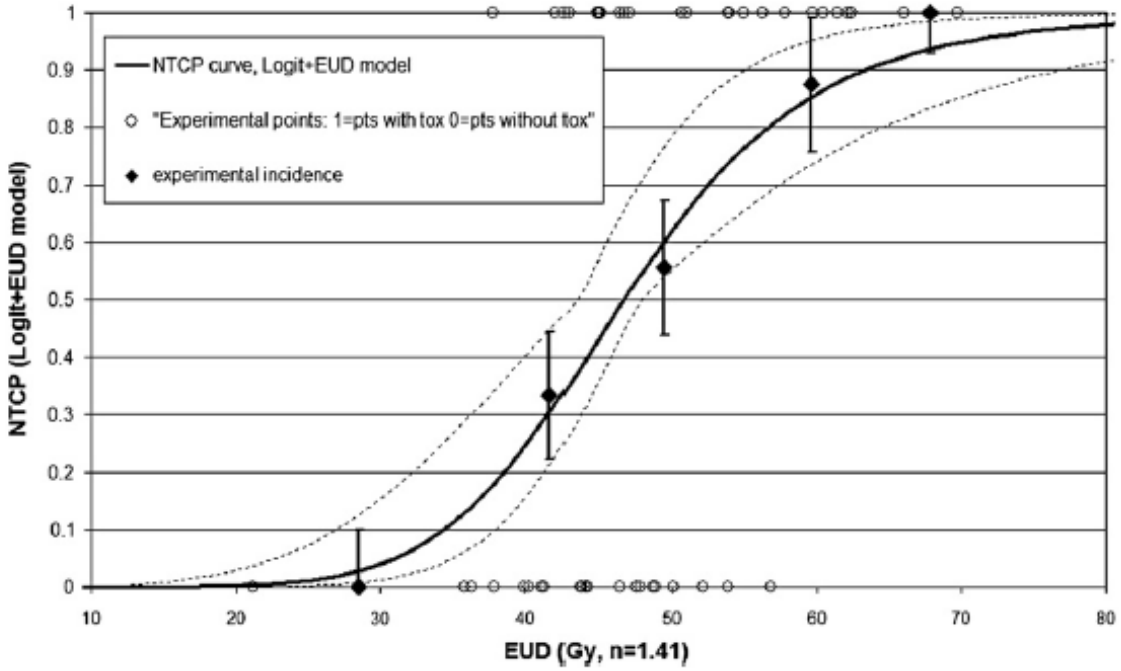


Fig (xi): *Plot of the probability of larynx oedema for irradiation of whole, two thirds, and one-third of the larynx (Lyman equivalent uniform dose [LOGEUD] normal tissue complication probability [NTCP] model*

Fung et al(51) conducted a study in non-laryngeal head and neck cancer patients who completed radiation therapy at least 12 months prior and was on follow up. The RT was by conventional 3 fieldsisocentric technique and treated using a 4 MV linear accelerator or cobalt-60. Patients with primaries of Tonsil, Soft palate, Vallecula, submandibular gland or unknown primary were included in the study. Patients with early glottic tumours were taken as the control group. The larynx was assessed using videostroboscopy, acoustic measurements and aerodynamic measurements after 12 months from completion of RT. The total RT dose delivered ranged from 60 to 74 Gy and the mean laryngeal dose was 50 Gy. Quality of life assessment was also done using VHI. All the patients were male and had a prior history of smoking. There was

increased supraglottic activity on videostroboscopy in the non-laryngeal group. 75% of the acoustic measures were worse in the non-laryngeal group including relative amplitude perturbation, amplitude perturbation quotient, normalized noise energy, pitch amplitude and spectral flatness ratio.

A study on voice quality on 43 patients with laryngeal or hypopharyngeal malignancies undergoing chemoradiation as part of larynx preservation protocol was conducted by **Carrara de-Angelis** et al(57). Total radiation dose delivered was 70.4 Gy. Radiation therapy was delivered by conventional planning methods. Voice was analysed perceptually by GRBAS scale by two independent observers and acoustically by 9 acoustic parameters. Perceptual analysis and acoustic analysis was done and showed normal results in 1 patient, mild dysphonia in 4 patients, moderate in 6 patients and severe dysphonia in 4 patients. The voice abnormalities were mild to moderate and allowed unintelligible communication in the studied group of patients.

A study from Korea by **Bae** et al(65), conducted in 127 patients with laryngeal and hypopharyngeal malignancies to assess the risk factors predictive of significant laryngeal oedema(SLE) by repeated flexible laryngoscopic examinations over a period of 2 years after completion of radiation therapy. The mean follow up was 35 months. Of these 127 patients, 2 (2%) underwent intensity-modulated radiotherapy (IMRT) and others underwent conventional external beam RT. The total prescribed dose Dmax <68 was correlated against various factors to find the association with significant laryngeal oedema. Significant laryngeal oedema was present in 44%. T classification was an independent predictor of significant laryngeal edema in multivariate analysis

(T1 vs. T2–4; odds ratio = 5.070, 95% confidence interval = 1.999–12.857; P = 0.001). Univariate analyses showed that tumour location, T and N classifications, overall stage, pathologic differentiation, and chemotherapy were significantly predictive of significant laryngeal oedema (P < 0.05). There was a recurrence of the tumour in 27%. Tumor recurrence rate was higher (39% vs. 7%, P < 0.001) and 3-year overall survival rate lower (54% vs. 87%, P < 0.001) in those with significant laryngeal edema as compared to those without SLE.

L. M. Dsouza Lawrence et al (66) conducted a study in 67 patients with non-laryngeal Head and Neck cancers undergoing IMRT to elucidate the predictors of laryngeal oedema. Patients underwent planning CT and a repeat CT at 6 to 7 weeks after initiation of RT to assess the absolute and relative change in the volume of the larynx. Mean cumulative laryngeal dose was calculated for each of the patients and was correlated with factors including age, sex, alcohol and tobacco use, primary site and stage, N stage, prior neck surgery, neoadjuvant chemotherapy and weight loss during treatment.

Mean (SD) initial and final volumes were 17.4 (3.7) and 20.0 (4.3) cc, respectively. The larynx increased in volume in all but 4 patients. The laryngeal volumes at planning were divided into tertiles. Mean (SD) per cent change from baseline was 15.7% (13.1%); the first and second tertiles were 7.5% and 20.6%, respectively. Increasing laryngeal volume at planning was directly correlated with, and the only predictor of those in the lower tertile. Increasing age was directly correlated with a swelling of the larynx in those in the higher tertile.

In a study by **Marcisano et al**(55), fifteen patients with early glottic cancer T_{is}-T_2N_0 was included. The radiation therapy was by conventional methods for 7 patients and with IMRT for eight of them. Laryngeal Vidoestroboscopy (LVS) of the larynx prior to and after radiation therapy at 0 to 4 months (acute), 4 to 12 months (subacute) and >12 months (chronic) was performed. The grading was done according to six parameters: vocal fold (VF) vibration, VF mobility, erythema/ oedema, supraglottic compression, glottic closure, and secretions. Grade, roughness, breathiness, asthenia, strain (GRBAS) voice perceptual scale was graded along with the LVS score by an observer. The radiation parameters studied were dose per fraction, number of fractions and overall treatment time. There were significant improvements in ipsilateral VF motion ($P = 0.03$) and vibration ($P = 0.001$) and significant worsening in contralateral VF motion ($P < 0.001$) and vibration ($P = 0.008$) at >12 months post-RT. Glottic closure significantly worsened, most prominent >12 months post-RT ($P = 0.01$). Composite GRBAS scores were significantly improved across all post-RT intervals. These results demonstrated that Laryngeal videostroboscopy can detect meaningful changes in VF and glottic function and support its use for post-RT evaluation of glottic cancer patients.

In a study by **Dornfield et al** (67), 27 patients with non-laryngeal head and neck carcinomas who underwent IMRT were studied. The total dose by IMRT was 66 to 70 Gy and the anterior neck field was delivered using conventional 4 MV beam to 50 Gy. Radiation doses delivered to various points along the upper aerodigestive tract, including the base of tongue, lateral pharyngeal walls, and laryngeal structures including pre-epiglottic space, aryepiglottic folds, false cords, lateral pharyngeal walls

at the level of false cords and upper oesophageal sphincter were recorded. Higher doses delivered to the aryepiglottic folds, false vocal cords, and lateral pharyngeal walls near the false cords correlated with a more restrictive diet, and higher doses to the aryepiglottic folds correlated with greater weight loss ($p < 0.05$) 1 year after therapy. Point dose should be less than 68Gy.

Correlation of DVH parameters with the voice-related quality of life

Vainshtein et al(44) from the University of Michigan conducted a study on 91 patients with stage III and IV oropharyngeal cancers, who underwent definitive chemoradiation with IMRT. The quality of life was assessed with the communication domain of HNQOL-C and speech questions in the UWQOL-S. The assessments were done prior to, and after radiation therapy till 24 months after completion of treatment. The radiation dose-volume parameters studied were Mean dose and V_{20} to V_{60}.

92% of patients were HPV positive. Median D_{mean} was 33.7 Gy. Mean glottic dose <20 Gy, 20 to 30 Gy, 30 to 40 Gy, 40 to 50 Gy and > 50 Gy was seen in 13, 24, 24, 11 and 19 patients respectively. Voice quality decreased maximally at 1 month, with 68% and 41% of patients reporting worse HNQOL-C and UWQOL-S scores compared with before treatment, and improved thereafter, recovering to baseline by 12 months when assessed with HNQOL-C and 18 months by UWQOL-S. Of patients with mean glottis dose <20 Gy, >20-30 Gy, >30-40 Gy, >40-50 Gy, and >50 Gy, 25%, 33%, 59%, 50%, and 64% reported worse voice quality at 6 months compared with pretreatment ($p<0.02$), which persisted at 12 months in 10%, 32%, 25%, 30%, and

63% of patients, respectively (P<.011).Univariate analysis revelaed that Mean glottic dose, N stage, neck dissection, oral cavity dose and time since chemoradiation was associated with voice or speech worsening. At multivariate analysis Mean glottic dose alone was associated.

In a study by **Dornfield et al**(67), mentioned above, QOL was assessed using HNCI QOL score before treatment and after 1 year. Better post-treatment speech Quality of life (QOL) scores were associated with lower doses delivered to structures within and surrounding the larynx.

Ma et al(68) was a retrospective comparison of patients with early glottic cancers who underwent transoral laser surgery versus conventional radiation therapy in terms of long-term voice outcome assessed objectively with both central spectral index and GRBAS scoring by two blinded speech pathologists and subjectively with the help of a VHI-10 questionnaire. The group who received RT had better GRBAS by 1.38 points and cepstral spectral index by 13.7 points ($p<0.01$).

Fung et al(51)as mentioned above, also assessed the voice quality of life with Voice handicap index (VHI) in his study. Voice handicap was significantly greater in the nonlaryngeal group in all three domains ($p<0.05$). When compared with patients receiving small field RT for early glottic tumours, there is objective and subjective evidence of vocal dysfunction in patients treated with wide-field RT for nonlaryngeal tumours.

Fung(69)conducted yet another study in patients with advanced laryngeal cancers, 46 of them with stage III and 51 with stage IV who underwent radical radiation therapy by a conventional method. After 1 cycle of induction chemotherapy with cisplatin 100 mg/m2 and 5 fluorouracil 1000mg/m2 Day 1 to 5, Patients were further randomized based on the response. Those with less than 50% response underwent early salvage laryngectomy, and patients with 50% or better response underwent concurrent chemoradiation (72 Gy and cisplatin 100 mg/m2 on Days 1, 22, and 43), followed by two cycles of adjuvant chemotherapy (CDDP/5-FU). All patients 8 weeks after chemoradiation underwent direct laryngoscopy and biopsy, and if there was residual disease underwent salvage laryngectomy. The voice quality of life was assessed with the V-RQOL questionnaire and List performance status scale for head and neck cancer patients (PSS-HN). Patients with an intact larynx demonstrated significantly higher (*p* - 0.02) mean V-RQOL scores (80.3) than did laryngectomy patients (65.4). This finding was consistent in the social-emotional (*p*-0.007) and physical functioning domains (*p* -0.03). No differences in V-RQOL scores were found in comparisons between early and late salvage laryngectomy. Predictors of a higher (better) V-RQOL score assessed by multiple linear regression model was low T stage, organ preservation and longer duration since treatment.

Ma et al(68)as mentioned above, also compared the voice quality of life between the TLM (Transoral Laser microexcision) and RT group. The mean V-RQOL scores for patients who had undergone radiotherapy (n=63), chemoradiotherapy (n=29), laser surgery (n=14), or total laryngectomy (n=27) as final treatment of laryngeal cancer

were 92.6, 92.9, 85.5, and 68.4, respectively; the mean VHI-10 scores were 2.87, 2.34, 5.43, and 11.26, respectively. The VRQOL and VHI-10 questionnaires are important in judging the overall effectiveness of treatment options for laryngeal cancer. There was no significant difference in VHI-10 between RT and TLM groups.

Oridate et al(70) conducted a study in 137 patients with laryngeal tumours who underwent TLM, RT, chemoradiation therapy and laser surgery who were followed up for a mean of 38 months. The radiation therapy was by conventional technique ≥60 Gy, generally 65 Gy. The total dose of RT was compared against the QOL scores for each group. The mean scores were 92.6, 92.9, 85.5 and 68.4 for RT, chemoradiation, laser surgery and TML groups respectively. (70)

Correlation of laryngeal oedema with QOL

Fung et al (51)compared voice function between two groups of patients who received radical radiation therapy, quantitatively by videostroboscopy, aerodynamic measurements and acoustic analyses. VHI score was used for the assessment of voice quality of life. It was found that the non-laryngeal cancer patients who received "wide field" RT had significantly worse voice quality of life and fared worse in the quantitative measurements as well. Patients with laryngeal early-stage cancer who received "small field" RT was used as a control in the study as the aim of the study was to assess the voice quality with RT in the previously unaffected larynx. This was more intriguing that these patients who received a higher dose to larynx had better QOL on follow up than non-laryngeal patients.

Methods and materials

Inclusion criteria:

(1) Patients undergoing locoregional radical radiotherapy or chemoradiotherapy with IMRT for non-laryngeal head and neck malignancies.

(2) No clinical symptoms or signs of laryngeal dysfunction.

Exclusion criteria

(1) Any tumour primarily involving the larynx or extending from other subsites.

(2) Any history of benign laryngeal pathology or surgical interventions in neck or larynx.

The patients who met the above-mentioned criteria underwent radiation treatment planning. Computerized Tomography 3mm cuts were taken from vertex to T4 level, with the patient in a supine treatment position, immobilized with a thermoplastic shell. The primary tumour volume (GTV p) and involved neck nodal levels (GTVn) were contoured. The clinical target volume and planning target volume was developed from the above. Brain, brainstem, spinal cord, eye, lens, cochlea, parotid gland, pharyngeal constrictors, lips, oral cavity, larynx, thyroid, heart, lungs, brachial plexus were contoured as critical organs. Brainstem, spinal cord, optic nerve and chiasm were also given margins to form corresponding PRVs (planning organ-at-risk volume)

The larynx contouring was done according to the protocol followed in RTOG 1016(71), outlined by Freedman et al(45). The volume defined as larynx is from the tip of the epiglottis superiorly to the bottom of the cricoid inferiorly; the external cartilage framework is excluded from the laryngeal volume.

Step one: Identify the most inferior edge of the hyoid bone and begin contouring on the next slice inferiorly.

Step two: The anterior boundary of the larynx contour is the inner surface of the thyroid cartilage.

In the superior portion of the contour, the posterior boundary of the larynx is taken as the lateral surfaces of the aryepiglottic folds and the posterior surface of the mucosa covering the arytenoids. The pyriform sinuses are not included in the larynx contour.

In the inferior portion of the contour, the posterior boundary of the larynx is the the posterior surface of the cricoid cartilage.

Step three: The most inferior extent of the larynx contour is the last image where the cricoid cartilage is seen as a complete ring.

All patient received radiation therapy as clinically indicated by the IMRT plan. Some patients receive radiation therapy as SIB, whereas others received it in sequential phases.

The radiation treatment of these patients was carried out according to the approved IMRT treatment plan after QA .

Dose Volume histograms (DVH) were developed for each IMRT plan. The dose volume parameters including maximum dose (D_{max}) and mean dose (D_{mean}) to the larynx, V_5 (the volume of larynx receiving 5 Gy), V_{10}, V_{15}, V_{20}, V_{25}, V_{30}, V_{35}, V_{40}, V_{45}, V_{50}, V_{55}, V_{60}, V_{65}, $V_{70}$and $V_{73.5}$ was estimated from the DVH. The Dmax was calculated as point dose (D_{max}) and Maximum dose received to 1cc (D_{max1cc}) of the laryngeal volume and was measured in centigray (cGy). The volume parameters measured the volume of the larynx receiving that particular mentioned radiation dose in Gy and was expressed in percentages as a percentage of the total laryngeal volume.

Laryngoscopy was performed at three time points: prior to initiation of radiation therapy, midway during radiation therapy (between 15^{th} and 18^{th} fraction) and at the end of radiation therapy. The dose volume parameters were compared with the laryngeal oedema grading assessed by flexible laryngoscopy at midway and at the end of radiation treatment.

The laryngeal oedema was graded according to the RTOG grading for laryngeal oedema as follows: 0, no oedema; 1, slight oedema; 2, moderate oedema; 3, severe oedema; and 4, necrosis.(72) Some degree of uncertainty is intrinsic to the subjectivity in the interpretation of ‘‘slight’’ and ‘‘moderate’’ in the RTOG scale. Grade 1 oedema would correspond to ‘‘minimal’’ thickening of the epiglottis, aryepiglottic folds, arytenoids, and false cords. Grade 2 is a more diffuse and evident oedema, although still without significant or symptomatic airway obstruction. The details are mentioned in Appendix-8.

The patients were also assessed subjectively for the quality of life by administering a V-RQOL questionnaire with 10 questions pertaining to voice and speech, each with a 5 point

Likert scale. The questionnaire was administered at the above mentioned time points as described for laryngoscopic assessment, i.e. prior to initiation of radiation therapy, midway during radiation therapy and at the end of radiation therapy.

The V-RQOL total score and subdomains- socioemotional and physical were calculated using the formulas (Appendix IV). Those with a V-RQOL score >75 to 100 were classified as excellent, 51 to 75 as Good, 26 to 50 as OK and less than or equal to 25 as poor according to Deshpande et al(63).

The scores were further grouped into excellent (more than 75) and non-excellent (less than or equal to 75) for the analytical purposes in this study.

All patients undergoing IMRT for non-laryngeal head and neck malignancies

↓

After the date of IRB approval of the study

↓

Baseline Laryngoscopy (L1)

V-RQOL questionnaire (Q1)

↓

IMRT planning

↓

Dose volume histograms created

↓

At midway of IMRT

Laryngoscopy (L2)

V-RQOL questionnaire (Q2)

↓

Completion of IMRT

↓

At completion,

Laryngoscopy (L3)

V-RQOL questionnaire (Q3)

↓

Computing the dose volume parameters:

Max dose, Mean Dose (Dmean)

V20, V30, V40, V50, V60, V70

↓

Analysis of the association of dose and volume with laryngeal oedema

↓

Analysis of the association of laryngeal dose with Quality of life score.

Statistical analysis:

With reference to Sanguineti et al(39), the mean laryngeal dose was 48.4 ±10 Gy. By assuming a standard deviation of 3.5, absolute precision of 3, with 95% confidence interval, the required sample size for the study was calculated as 31.

Data was entered using EPIDATA software. Data was screened for outliers and extreme values using Box-Cox plot and histogram (for the shape of the distribution). Patient characteristics are expressed as mean and standard deviations or median and interquartile range (IQR) for continuous variables, frequencies, and percentages for categorical variables. The difference in baseline patient demographics and clinical characteristics were compared using Pearson chi-square tests for categorical variables and Student *t* tests or Mann-Whitney *U* test, when appropriate, for continuous variables. ROC analysis (Quality score) was done to find the best cutoff value of dose-volume variables. Statistical analyses were performed using SPSS 25 software.

Results

1. DEMOGRAPHIC DETAILS

Age: There was a total of 31 patients out of which 19 (61.29%) were ≤50 years and the remaining 12 (38.70%) were >50 years of age. Mean age was 46.19± 12.8 years.

Gender: 27 (87.1%) were males and 4 (12.9%) were females.

Geographical distribution: It was comparable between different regions of India namely North Indian, North East Indian, South Indian and other groups (including those from Bangladesh) as 32.3%, 19.4%, 22.6% and 25.8% respectively.

Habits: Nine (29%) patients gave a history of tobacco smoking. 11 (35.5%) of them had a history of using smokeless tobacco or pan chewing. None of them has a history of alcohol abuse.

Primary sites: Eighteen (58.1 %) of the patients had a nasopharyngeal primary. There were six (19.4%) patients with carcinoma oropharynx and three (9.7%) patients with sinonasal carcinoma. There was one (3.2%) patient each with oral cavity, carcinoma maxilla, olfactory neuroblastoma and others.

Histology: The most common histological diagnoses of these patients were undifferentiated carcinoma (nine- 29%), poorly differentiated carcinoma (eight- 25.8%) and poorly differentiated squamous cell carcinoma (five- 16.1%).

TNM staging: Most of the tumours were T4a (thirteen- 41.9%), followed by T3 (seven- 22.6%). There were four (12.9%) T2 tumours and five (16.1%) T1 tumours. Only one (3.2%) patient has T4b lesion.

Most common nodal stage was N2a (eleven – 35.5%) followed by N0 (eight – 25.8 %) and N2b (five – 16.1%). There were three (9.7%) each patient with N1 and N2c stages, and one (3.2%) patient with the N3 stage.

In total, there were 8 (25.8%) node negative and 23 (74.2%) node-positive patients.

The most common overall stage was IVA (fifteen – 48.4%) followed by III (nine – 29%) and IV B (six – 19.4%). Only one (3.2%) patient was stage II.

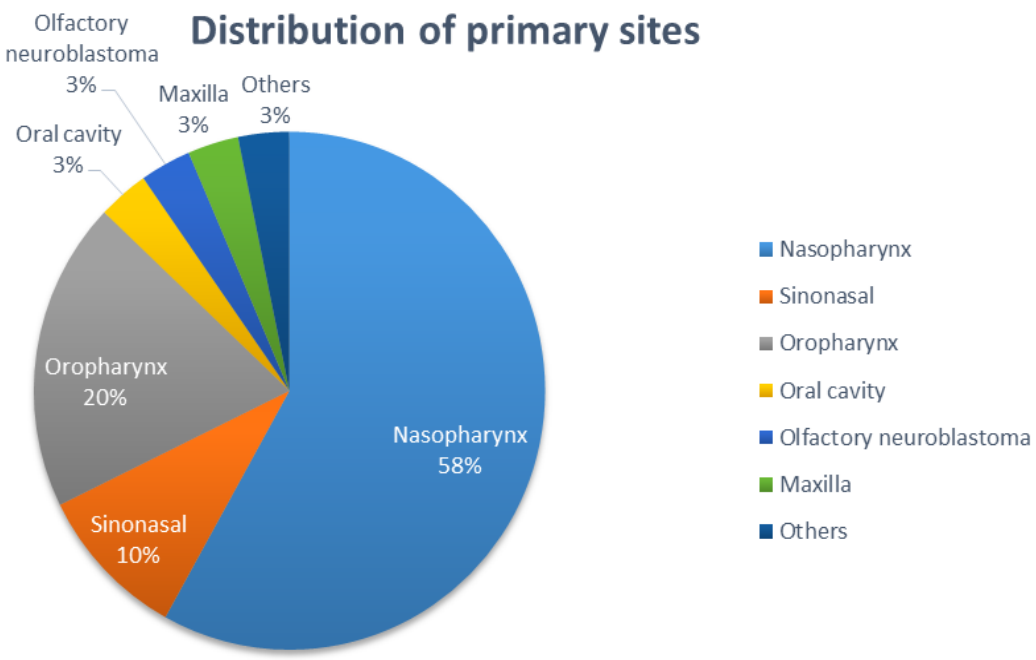


Fig (xii) showing the distribution of primary sites of malignancy among the patients.

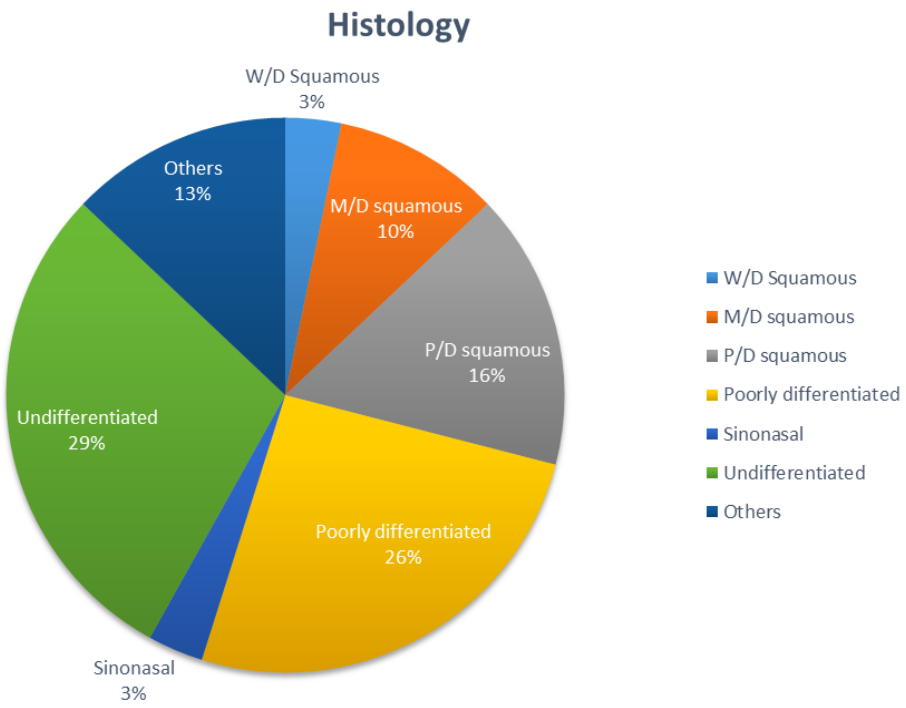


Fig (xiii): Distribution of different histologies reported among the patients

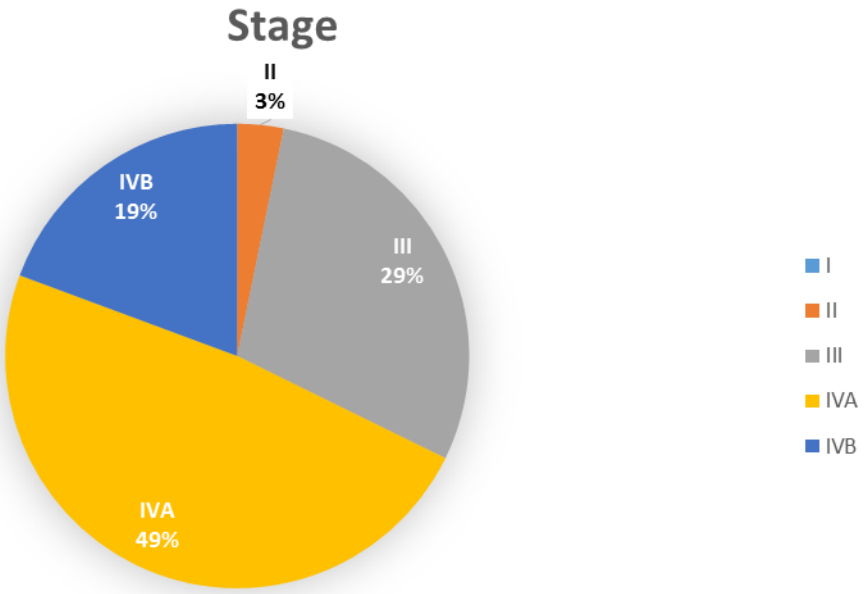


Fig (xiv): Stage-wise distribution among the patients

Clinical Symptoms: Four (12.9%) patients had dysphagia as their presenting symptom, whereas nine (29%) had a nasal blockade and four (12.9%) had ear blockade. Eight (25.8%) of them had throat pain and five (16.1%) had an ulcer in the mouth. Five (16.1%) had nasal bleed and one (3.2%) had hoarseness as their presenting complaint. Eighteen (58.1%) of them had one or more swellings in the neck as a presenting complaint.

Comorbidities: Six (19.4%) of them were diabetic and six (19.4%) were hypertensive. Eight (25.8%) has had some surgery in the past, but none with the history of surgery in the neck or throat.

Performance status: The performance scale assessed with ECOG was 1 for all patients.

Anthropometric details: The mean weight and height of the patients were 60.26 ± 12.8 kilograms and 162.06 ± 6.68 centimetres. The average BMI was 22.93± 4.48 kilogram per square metres. There were a significant weight loss of > 10 % in two (6.45%) patients only.

Radiation therapy and Chemotherapy details:

Seven (22.6 %) of the patients received radiation therapy as adjuvant whereas for rest 24 (77.4 %) of them the intent was radical.

With regards to temporality, 8 (25.8%) of them sequential whereas 19 (61.3%) of the radiation plans were a simultaneous integrated boost. 4 (12.9%) of them had radiation as a single phase.

12 (38.7%) patients received three cycles of neoadjuvant chemotherapy followed by concurrent chemoradiation therapy, whereas 15 (48.4%) of them received upfront chemoradiation therapy. 4 (12.9%) of them did not receive any chemotherapy.

In total 27 (87.09%) patients received concurrent chemotherapy.

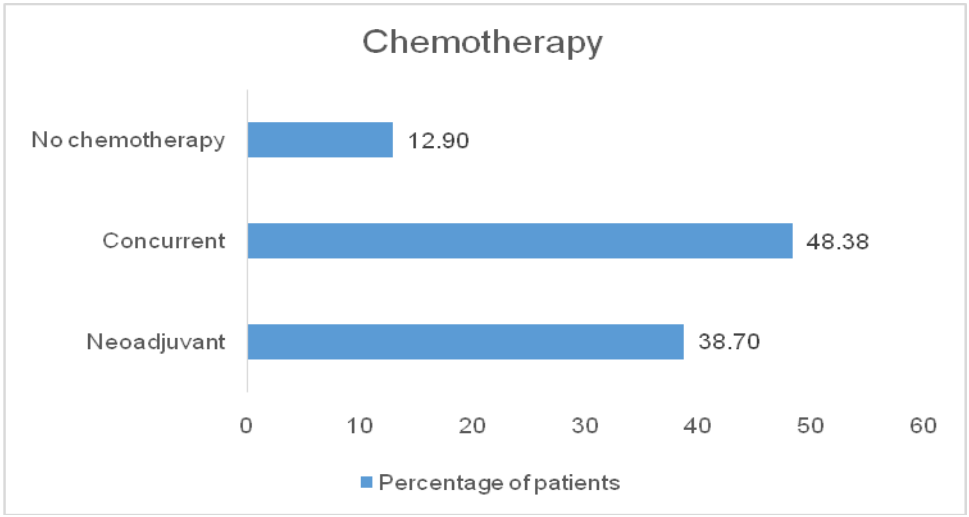


Fig (xv): Types of chemotherapy

2. RESULTS OF RADIATION DOSE AND VOLUMETRIC CHARACTERISTICS

The mean total radiation dose (TD) delivered was 67.54± 3.96 Gy. The mean laryngeal D_{max} was 62.66 ± 11.41 Gy. The mean maximum dose received to 1cc of the larynx (Dmax 1cc was 53.47 ± 14.53 Gy. The mean laryngeal dose was 45.10 ± 14.14 Gy.

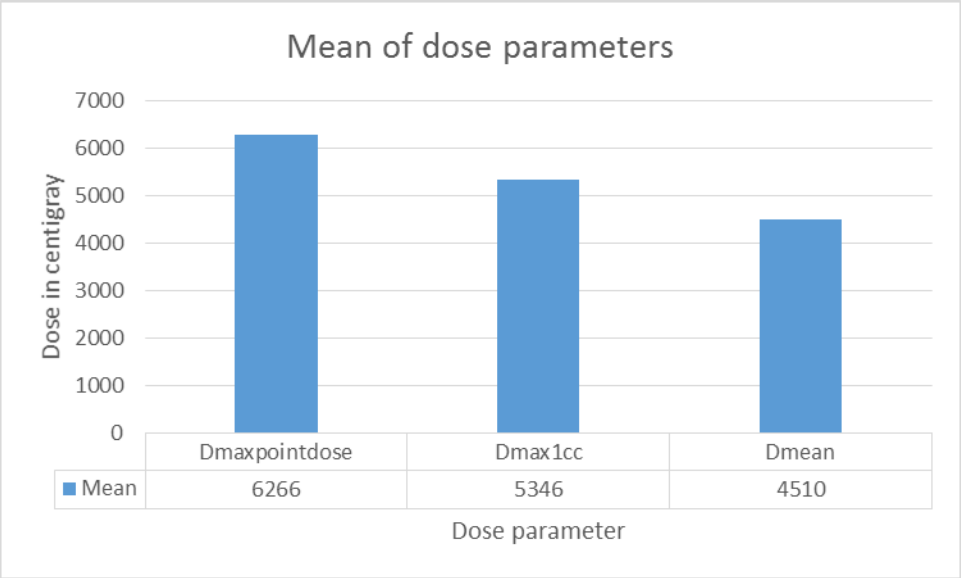


Fig (xvi): Mean ± standard deviation values of different dose parameters of all patients

The mean volume parameters V5, V10, V15, V20, V25, V30, V35, V40, V45, V50,V55,V60,V65,V70 and V73.5 were 94.23%, 91.82%, 91.14%, 90.67%, 89.57%, 86.58%, 80.56%, 71.74%, 61.12%, 46.1%, 29.33%, 11.35%, 4.23%, 0.99% and 0% respectively.

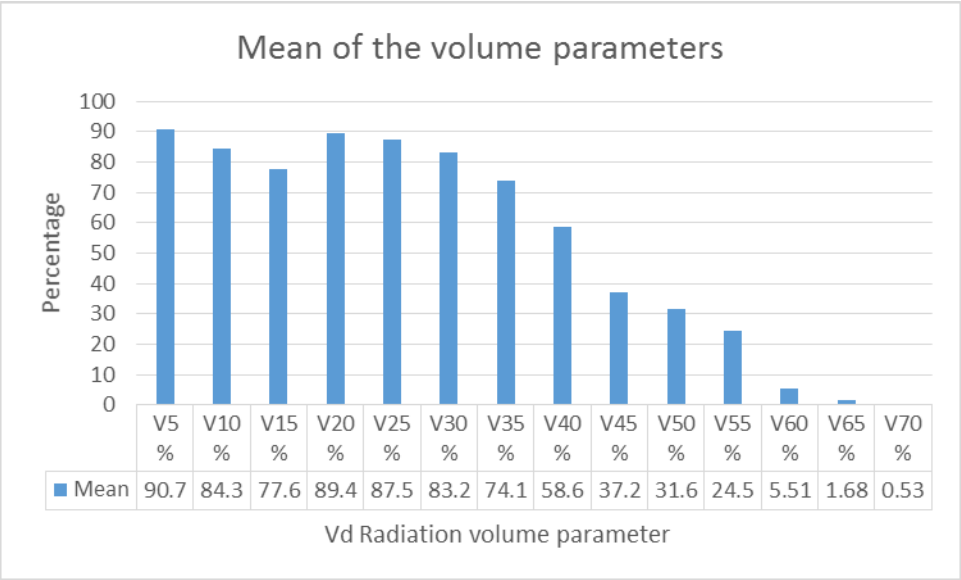


Fig (xvii): Mean ± standard deviation of the volume parameters of all patients

3.RESULTS OF LARYNGOSCOPY ASSESSMENT

All patients had normal laryngoscopy findings prior to radiation therapy.

Midway during radiation 23 (73.2%) of them had grade 1, while 2 (6.25%) of them had grade 2 laryngeal oedema and 5 (16.1%) of them did not have any laryngeal oedema.

At the end of radiation therapy, 23 (71.87%) of them had grade 1, whereas 6 (19.4%) of them had grade 2 (6.25%) laryngeal oedema and 2 (6.25%) of them did not have laryngeal oedema.

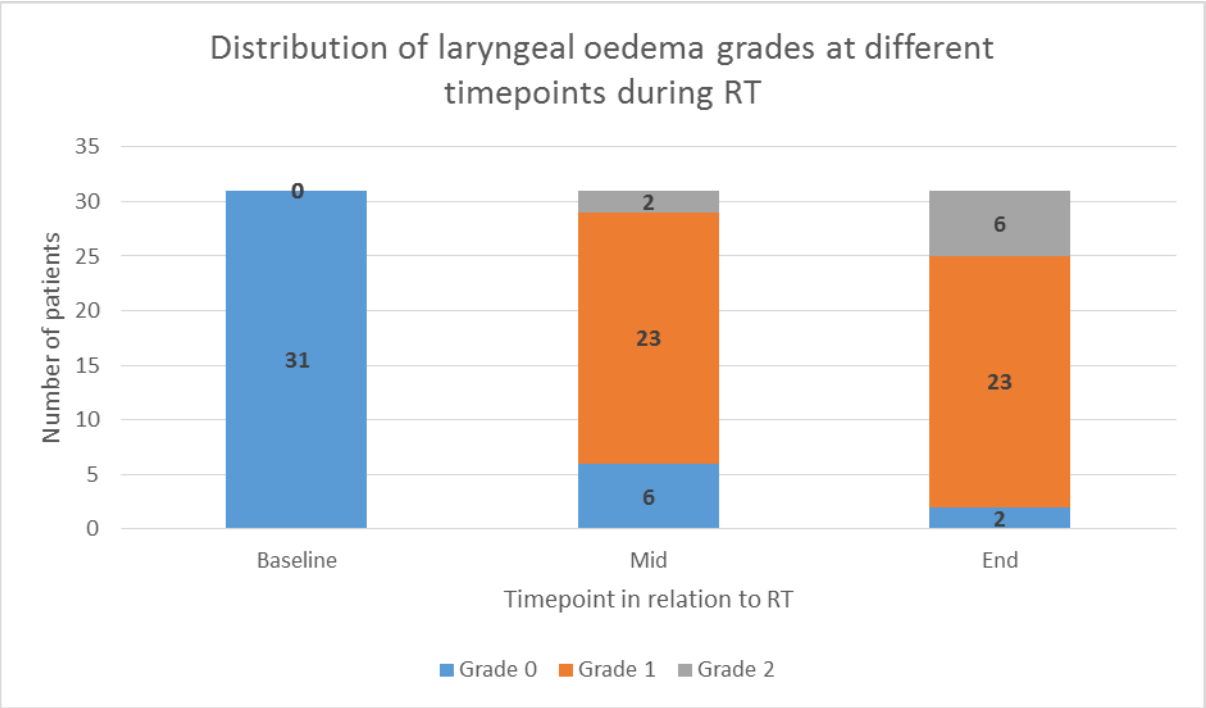


Fig (xviii): Distribution of laryngeal oedema at different time points, i.e. prior to, during and at end of radiation therapy

4.RESULTS OF V-RQOL QUESTIONNAIRE

The mean baseline V-RQOL total score was 99.27 ± 1.84. The total scores at midway and end of radiation therapy dropped to 82.67 ± 20.37 and 69.03 ± 19.86 respectively.

The V-RQOL socioemotional scores prior to, midway and end of radiation therapy were 100 ± 0, 86.69 ± 20.07 and 76.41 ± 22.69 respectively. The physical V-RQOL scores prior to, midway and end of radiation therapy were 98.79 ± 3.07, 80.24 ± 21.88 and 64.38 ± 20.35 respectively.

Table (II): The mean V-RQOL total and subdomain scores of all patients at different time points during radiation therapy

V-RQOL score/ Time points	Prior to RT	Midway during RT	End of RT
Total	99.27±1.84	82.67 ±20.37	69.03 ±19.86
Socioemotional	100 ± 0	86.69 ± 20.07	76.41 ± 22.69
Physical	98.79 ± 3.07	80.24 ± 21.88	64.38 ± 20.35

Ten (32.3%) patients had a V-RQOL total score less than 75 at midway assessment. But this increased to 17 (54.8%) at the end of radiation therapy.

Eight (25.8%) had a V-RQOL socioemotional score less than 75 at midway during radiation therapy which increased to 15 (49.4%) at end of RT.

Ten (32.3%) had V-RQOL physical scores less than 75 at midway during radiation therapy, which increased to 26 (83.9%) at end of RT.

5. **CORRELATION OF RT DOSE VOLUMETRICS AND LARYNGEAL EDEMA (ASSESSED BY LARYNGOSCOPY)**

Two (6.5%) patients had grade≥2 oedema at midway during radiation therapy, and six (19.4%) had grade≥2 oedema at the end of radiation therapy.

The mean values of DVH parameters of those patients who had grade 2 oedema versus grade 1 were as follows:

Table (III): Dose and volume parameters of patients with Laryngeal oedema grade 1 and 2 separately

	Grade 1	Grade 2
Laryngeal volume	12.4478 cm3	13.4908
Dmax	6224.5	6659.7
Dmax 1cc	5437.37	5214.19
Dmean	4473.58	4761.15
V5	92.68	98.27
V10	90.15	95.50
V15	89.43	94.74
V20	88.94	94.17
V25	87.6	93.65
V30	84.37	92.88
V35	79.85	86.20
V40	72.82	73.62
V45	63.16	60.93
V50	47.59	47.99
V55	30.6	32.09
V60	10.06	20.08
V65	2.71	11.47
V70	0.96	1.43
V73.5	0	0

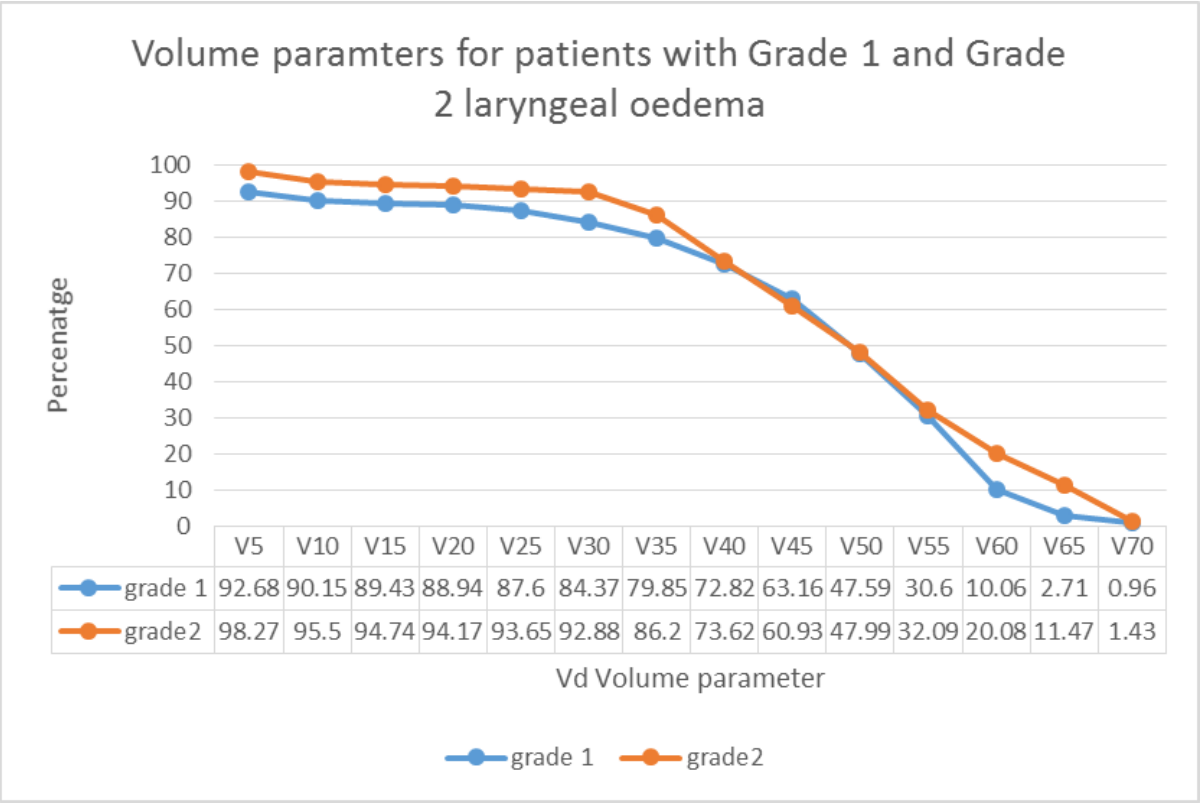


Fig (xix): Line diagram showing the values of various volume parameters for patients who developed grade 1 and grade 2 laryngeal oedema separately

There was a significant association between laryngeal oedema grades at end of RT (≤ 1 versus >2) with V65 (p=0.028). It was found that when V65 was less than 1%, there was significantly less chance of grade≥ 2 oedema to occur. (Sensitivity 78.6%, specificity 41.2%, AUC 0.628)

There was no association seen between laryngeal oedema and other dose-volume parameters at the end of radiation therapy.

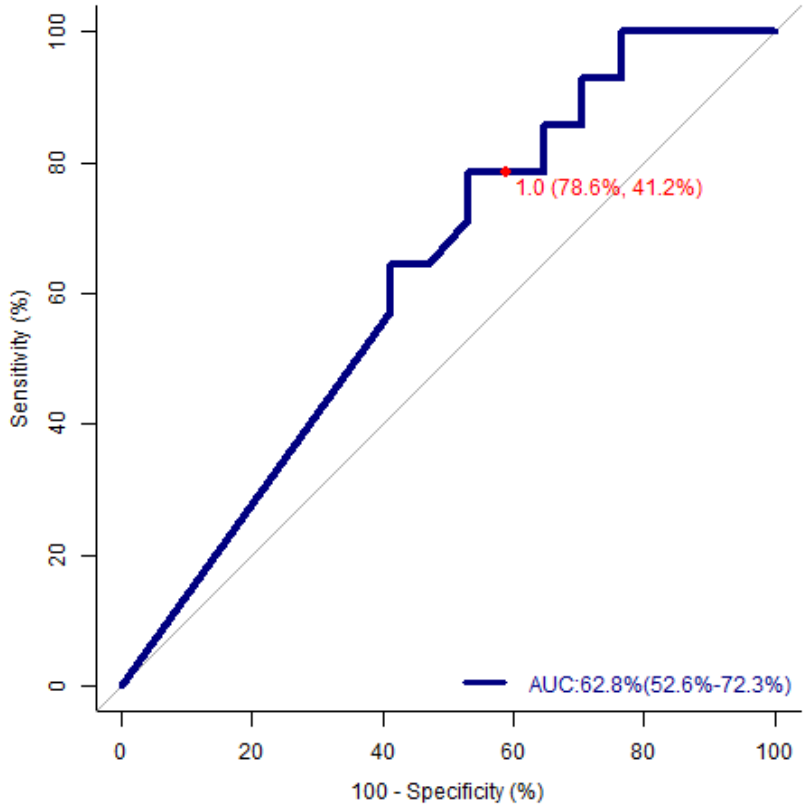


Fig (xx): ROC curve to define the value of V_{65} causing grade ≥2 laryngeal oedema.

6. CORRELATION OF RT DOSE VOLUMETRICSWITH VOICE RELATED QUALITY OF LIFE (ASSESSED WITH V-RQOL QUESTIONNAIRE)

The values of different DVH parameters for those with the total V-RQOL score at end of radiation therapy <75(non-excellent) and >75 (excellent) were as follows:

Table (IV): Values of dose and volume parameters for patients with a V-RQOL total score < 75 and >75 separately

	Total V-RQOL >75	Total V-RQOL <75
Laryngeal volume	13.14	12.06
Dmax	6337.1	6207.9
Dmax 1cc	5472.14	5244.2
Dmean	4353.17	4640.07
V5	93.91	94.49
V10	90.51	92.89
V15	89.71	92.30
V20	88.98	92.05
V25	87.55	91.24
V30	83.62	89.01
V35	77.61	82.98
V40	68.50	74.39
V45	56.48	64.94
V50	42.71	48.89
V55	25.67	32.35
V60	6.51	15.35
V65	1.26	6.57
V70	0.32	1.53
V73.5	0	0

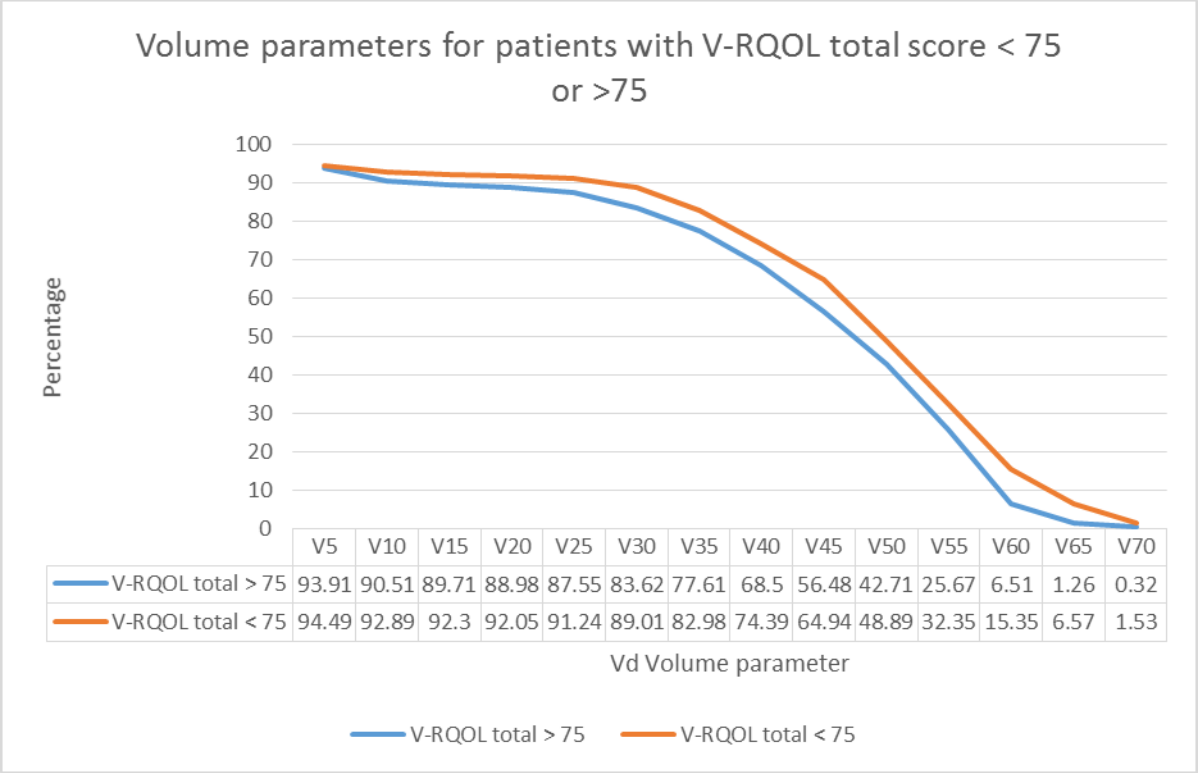


Fig (xxi): Volume parameters for patients with V-RQOL total scores <75 and >75 separately

When the V-RQOL total score of all patients are clubbed into two groups as <75 and >75, there was a statistically significant difference in V60, V65 and V70. The V-RQOL score was >75 when the V60 (sensitivity 76%, specificity 36% and AUC 0.592), V65 (sensitivity 41.2%, specificity 78.6%, AUC 0.628) and V70 (sensitivity 17.6%, specificity 92.9%, AUC 0.553) were less than 1 %.

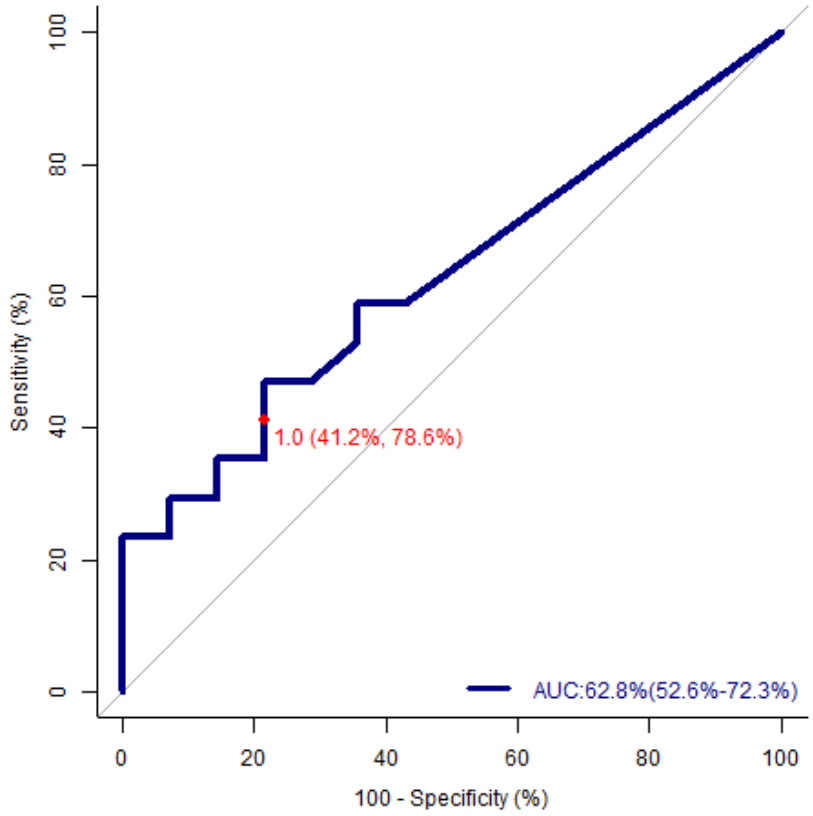


Fig (xxii): ROC curve to define the value of V_{65} causing the V-RQOL total score to be less than 75.

The values of different DVH parameters for those with a socioemotional domain of V-RQOL score at end of radiation therapy <75 (non-excellent) and >75 (excellent) were as follows:

Table (V): Values of dose and volume parameters for patients with V-RQOL socioemotional scores <75 (non-excellent) and >75 (excellent) *separately*

	Socioemotional V-RQOL >75 (excellent)	Socioemotional V-RQOL <75 (non-excellent)
Laryngeal volume	12.76	12.32
Dmax	6067.3	6478.4
Dmax 1cc	5223.1	5479.4
Dmean	4185.82	4856.82
V5	89.47	99.31
V10	85.84	98.20
V15	84.80	97.89
V20	84.10	97.65
V25	82.84	96.74
V30	79.42	94.21
V35	74.16	87.38
V40	66.20	77.65
V45	55.47	67.15
V50	43.06	49.34
V55	27.17	31.63
V60	7.60	15.35
V65	1.14	7.52
V70	0.28	1.14
V73.5	0	0

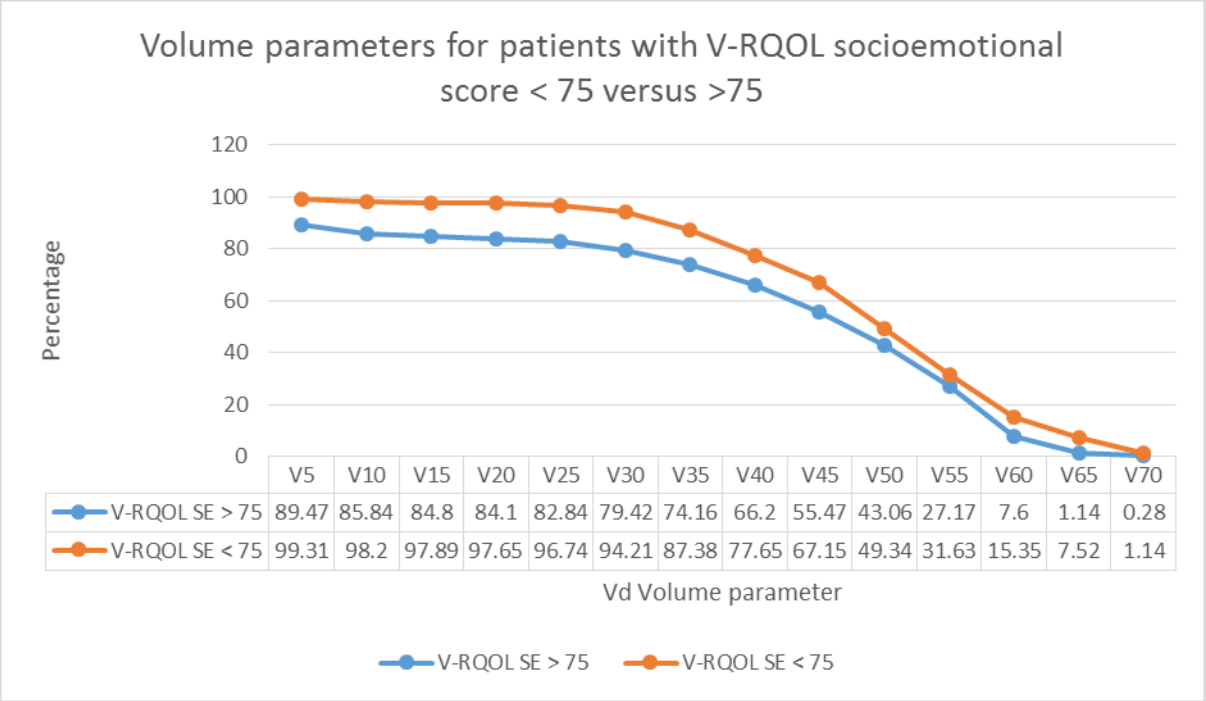


Fig (xxiii): Volume parameters for patients with V-RQOL socioemotional scores < 75 and >75 separately.

For the socio-emotional domain of the V-RQOL score, the difference between groups with a score<75 and >75 was significant with regard to D_{mean}, V5, V10, V15, V20, V25, V30, V35, V60, V65 and V70.

The following given are the cut off values of volume parameter for the V-RQOL socioemotional score to be >75 or excellent. In parentheses are the sensitivity, specificity and AUC respectively:

V20 < 100% (86.7%, 43.8%, 0.656)

V30 < 100% (86.7%, 50%, 0.679)

V35 <26% (100%, 25%, 0.596)

V40 <10% (100%, 25%, 0.593)

V50 <6% (86.7%, 31.2%, 0.562)

V60 <3% (53.3%, 50%, 0.39)

V70 < 1 % (20%, 93.8%, 0.585)

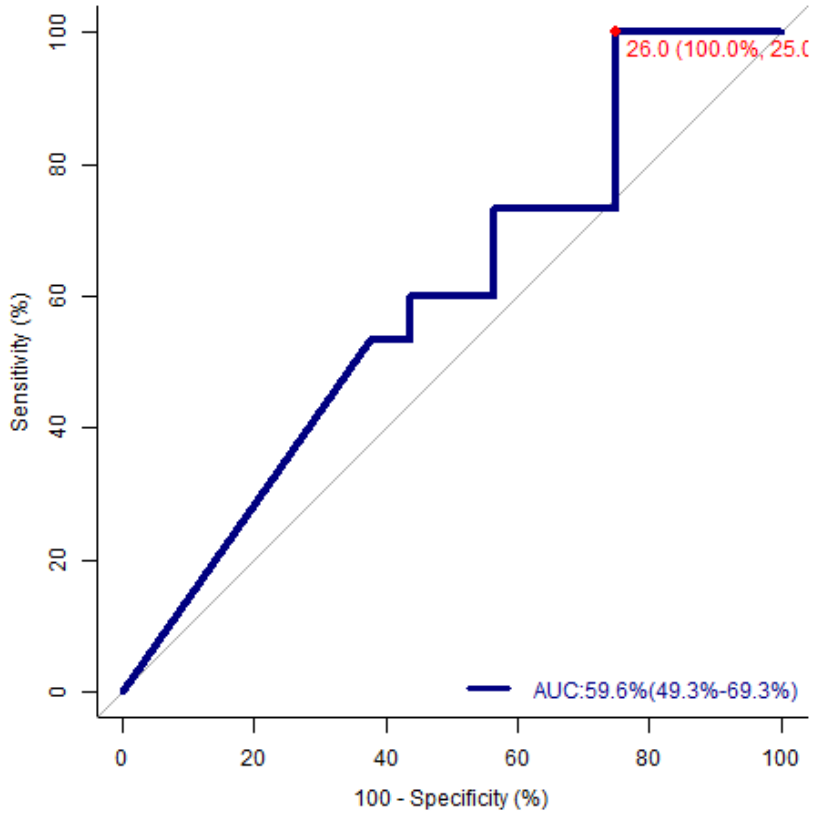


Fig (xxiv): ROC curve to define the value of V_{35} causing V-RQOL socioemotional score to be less than 75.

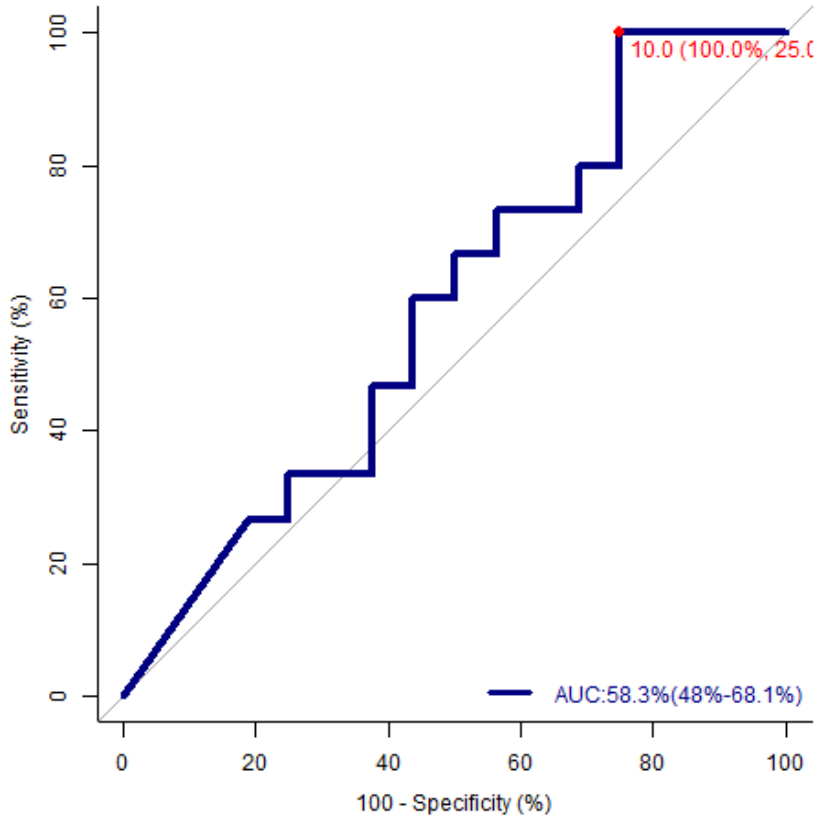


Fig (xxv): ROC curve to define the value of V_{40} causing the V-RQOL socioemotional score to be less than 75.

The values of different DVH parameters for those with a physical domain of V-RQOL score at end of radiation therapy <75 (non-excellent) and >75 (excellent) were as follows:

Table (VI): Values of dose and volume parameters of patients with V-RQOL physical scores < 75 and > 75 separately

	Physical V-RQOL >75	Physical V-RQOL <75
Laryngeal volume	15.01	12.08
Dmax	6337.1	6207.9
Dmax 1cc	5472.14	5244.2
Dmean	4353.17	4640.07
V5	93.91	94.49
V10	90.51	92.89
V15	89.71	92.30
V20	88.98	92.05
V25	87.53	91.24
V30	83.62	89.01
V35	77.61	82.98
V40	68.50	74.39
V45	56.48	64.94
V50	42.71	48.89
V55	25.67	32.35
V60	6.51	15.35
V65	1.26	6.57
V70	0.316	1.53
V73.5	0	0

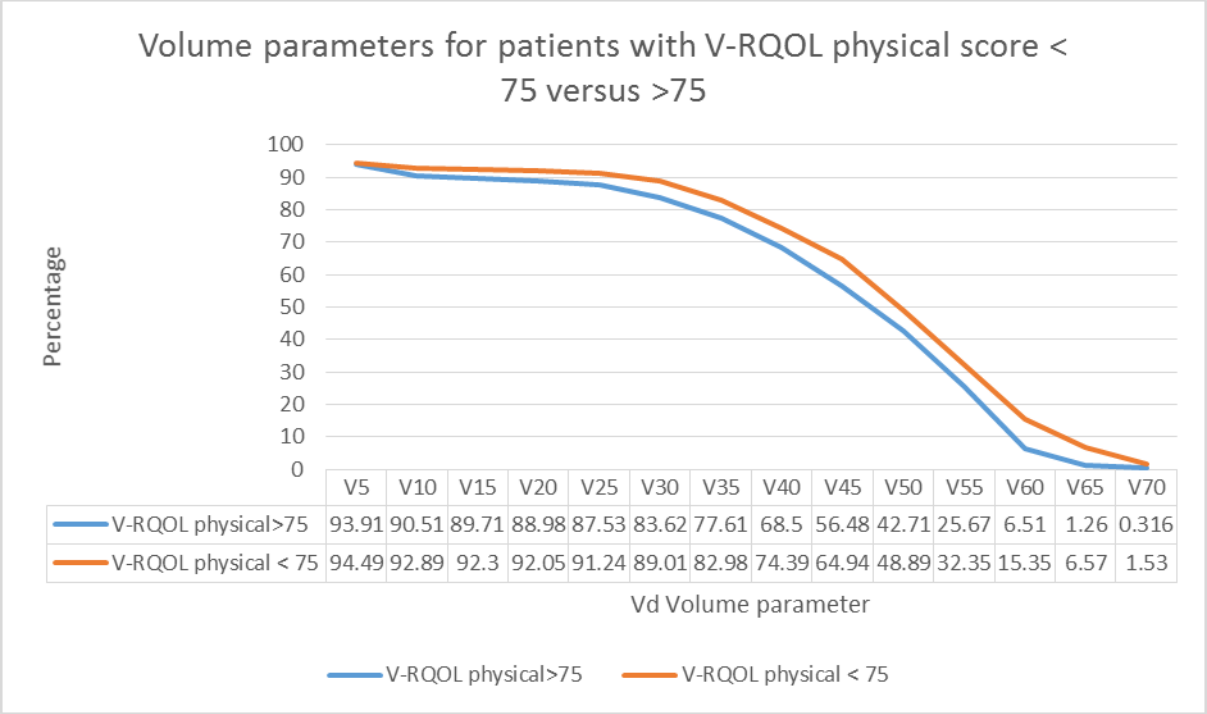


Fig (xxvi): Volume parameters for patients with V-RQOL physical scores <75 and >75 separately

For the physical domain of V-RQOL score, this was significant only for V65. When V65 was less than 1% (sensitivity 38.5%, specificity 100%, AUC 0.715)

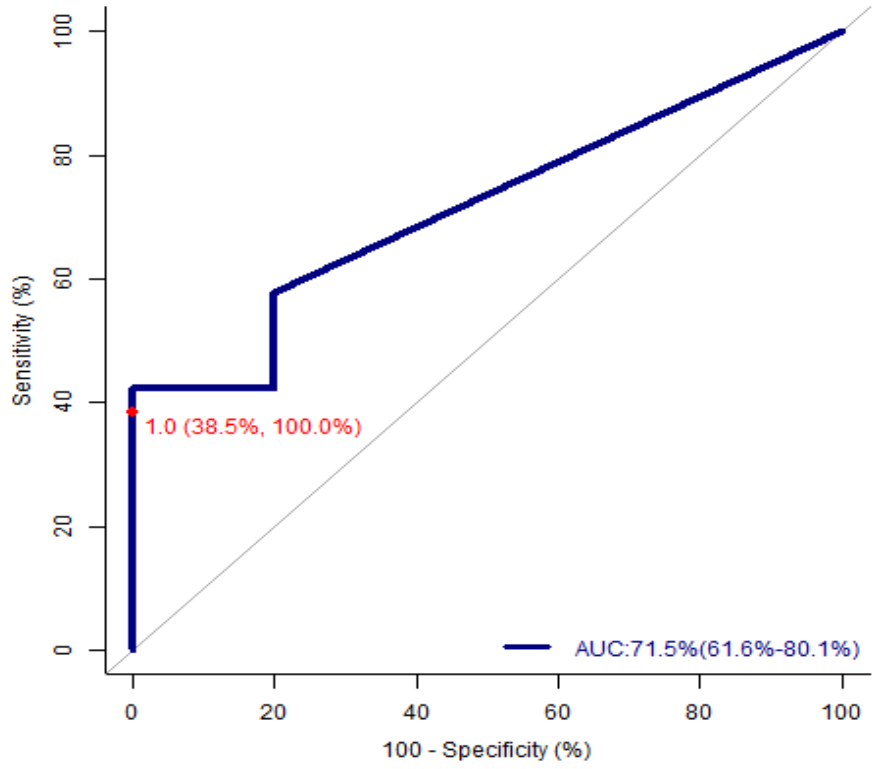


Fig (xxvii): ROC curve to define the value of V_{65} causing the V-RQOL physical score to be less than 75.

When the ungrouped individual V-RQOL scores of each of the patients were compared against dose-volume parameters there was no significant correlation.

7. CORRELATION OF VOICE RELATED QUALITY OF LIFE WITH LARYNGEAL EDEMA (ASSESSED BY LARYNGOSCOPY)

Table (VII) shows the V-RQOL scores at end of radiation therapy (expressed as Mean ± SD) for those with laryngeal oedema less than and more than Grade 2 separately

V-RQOL scores	Time point	Laryngeal oedema		P value
		Grade 1	Grade 2	
V-RQOL score total	Midway	83.97 ± 0.43	63.75 ± 1.77	NS
	At end	74.4 ± 17.42	46.67 ± 12.81	0.001
V-RQOL score socioemotional	Midway	87.28 ± 20.49	78.13 ±13.26	NS
	At end	82.5 ± 19.09	51.04 ± 19.53	0.001
V-RQOL score physical	Midway	81.47 ± 22.09	62.50 ± 5.90	NS
	At end	69.33 ± 18.71	43.75 ± 13.11	0.004

As shown in the table, there was a significant correlation between laryngeal oedema and quality of life scores at the end of radiation treatment. But at midway during radiation therapy, there was no significant correlation between laryngeal oedema and

V-RQOL score groups. When the V-RQOL scores were regrouped into excellent versus (non-excellent) others also, significance was seen only at the end of radiation therapy.

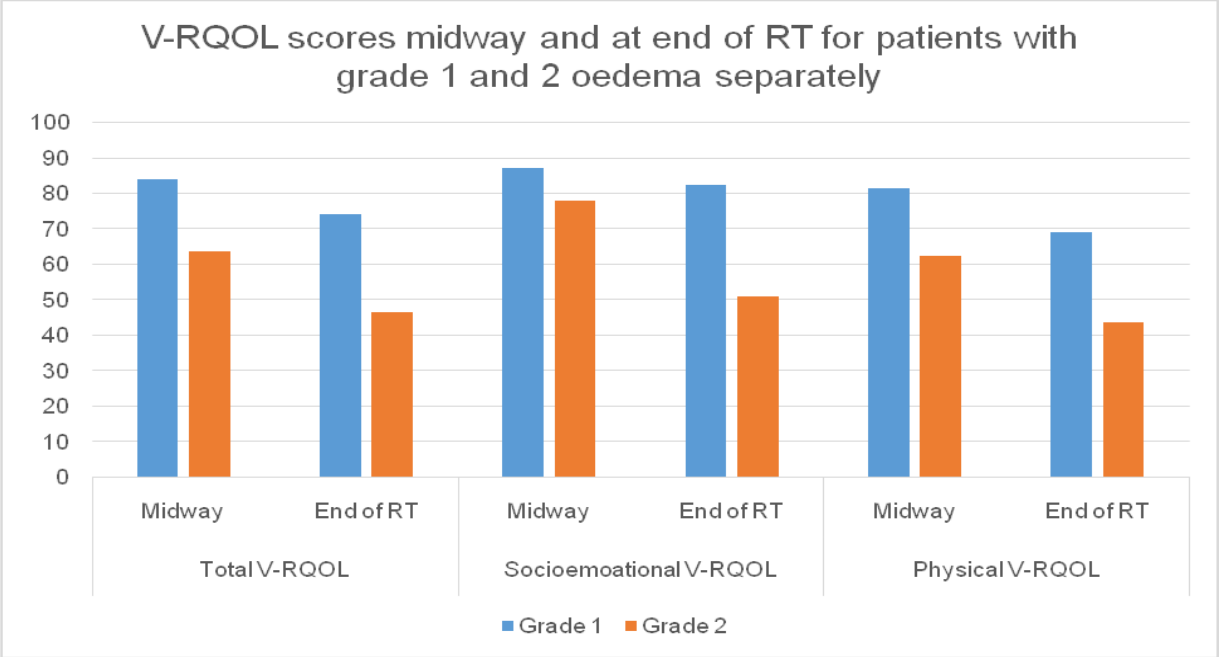


Fig (xxviii): Total and subdomain V-RQOL scores midway and at end of RT for patients with grade 1 and 2 oedema separately

Table (VIII) below depicts the number of patients with grade > 2 oedema among those whose V-RQOL scores dropped below 75 for each domain.

V-RQOL SCORES <75	No of patients with Laryngeal oedema	
	Grades <2	Grade≥ 2
V-RQOL score total<75	11 (64.7%)	6 (35.3%)
V-RQOL score socioemotional <75	9 (60%)	6 (40%)
V-RQOL score physical <75	20 (76.9%)	6 (23.1%)

(Percentage values given in parentheses are within a row)

8. SUBGROUP ANALYSIS

Age:

12 (38.70%) patients were more than 50 years. Four patients (33.3%) among those more than 50 years had grade 2 laryngeal oedema. 19 (61.2%) patients were less than 50 years, and two (10.52 %) of them had grade 2 laryngeal oedema.

In the more than 50 years group, seven (58.3%) of the 12 patients had a V-RQOL score equal to 75, while the rest five (41.66%) had an excellent V-RQOL score at the end of radiation therapy. While in the < 50 years group, 17 (89.47%) of the 19 had V-RQOL less than 75.

The mean age of those with V-RQOL < 75 was 48.80 years versus those with an excellent V-RQOL had a mean age of 43.75 years.

There was no significant difference between the quality of life or laryngeal oedema at end of radiation therapy between the different age groups.

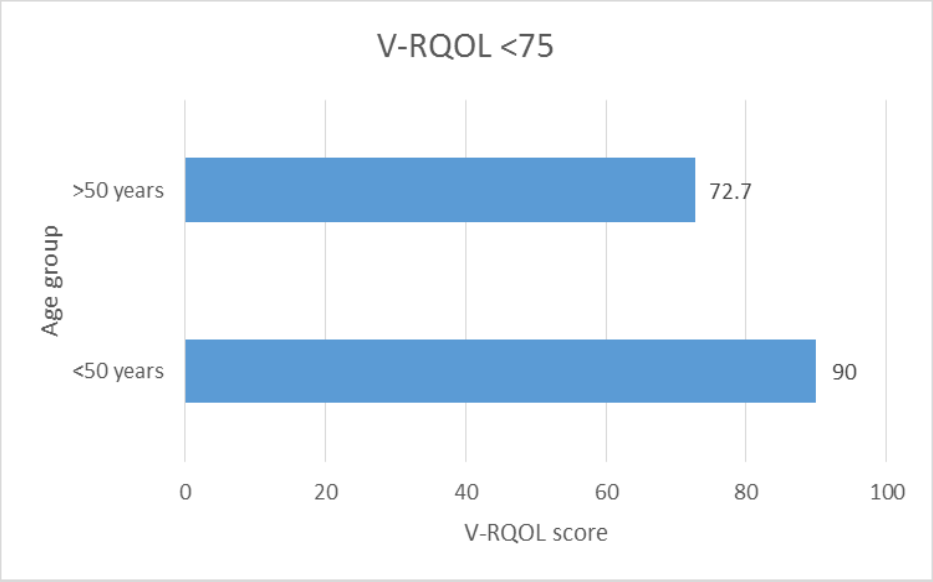


Fig (xxix): Percentage of patients with V-RQOL Total score values <75 in age groups <50 and >50 separately

Laryngeal volume:

The mean laryngeal volume of all patients was 12.55 cm^3.

Those with grade 2 oedema had a mean volume of 13.49 cm^3 while those with grade 1 oedema who had smaller mean laryngeal volume 12.44 cm^3.

Those with a V-RQOL score >75 had a mean laryngeal volume of 13.14 cm^3 versus those with <75 had 12.06 cm^3.

There was no significant difference between laryngeal oedema grades or V-RQOL scores with the initial volume of the larynx.

Chemotherapy:

4 (33.3%) out of 12 who underwent neoadjuvant chemotherapy had grade 2 laryngeal oedema, while 2 (10.53%) of the 19 who did not receive chemotherapy had laryngeal oedema.

For those who did not undergo neoadjuvant chemotherapy, the total V-RQOL score at the end of radiation therapy was 71.18, as compared to those who underwent neoadjuvant chemotherapy had a lower score of 65.63. Similarly, the V-RQOL socioemotional and physical scores at the end of RT were 78.95 and 66.01 for those

who did not receive neoadjuvant chemotherapy versus lower scores of 72.40 and 61.80 for those who did.

6 (22.2%) of the 27 patients who received concurrent chemotherapy, whether upfront or after neoadjuvant, had grade 2 oedema, while none of the four who did not receive chemotherapy had grade 2 oedema.

There was no significant difference between V-RQOL scores and laryngeal oedema grades of those who received or did not receive neoadjuvant or concurrent chemotherapy.

Weight loss:

Two (6.45%) had a significant weight loss of more than 10%. Both had grade 1 laryngeal oedema at end of RT. While both patients had an excellent quality of life scores during the midway assessment, one of them fared poorly at the end of RT with a V-RQOL score of 37.5.

There was no significant difference between laryngeal oedema grades or V-RQOL scores with weight loss during therapy.

Primary site: The primary sites were divided into groups as Nasopharynx, Oropharynx and others. There was no significant difference between laryngeal oedema grades or V-RQOL scores with different primary sites.

Nodal involvement: The patients were divided into two groups N0 (no nodal involvement) and N+ (those with significant nodal involvement).

Out of the 8 node-negative patients, 1 (3.22%) patient had grade 2 oedema and 6 (19.35%) had grade 1 at the end of radiation therapy. Among the node-positive patients, 5 (16.12%) had grade 2 oedema, 24 (77.41%) had had grade 1 oedema.

Among the node-negative patients, four (50 %) of them had V-RQOL total scores at the end of radiation to be less than 75, whereas this was 13 (56.5 %) out of 23 patients with node-positive status.

There was no significant difference during RT and at the end between the incidence of laryngeal oedema or V-RQOL score groups in total, socio-emotional and physical domains.

9. EFFECT OF ORAL CAVITY DOSE ON V-RQOL

There was a significant difference of oral cavity D_{mean} and D_{max_1cc} at midway during radiation therapy, between V-RQOL total score groups (Excellent > 75 versus others < 75). Similarly, a significant difference was seen for both D_{mean} and D_{max_1cc} at midway between groups of the physical domain of the V-RQOL. But a significant

difference was seen only for D_{max_1cc} at midway between groups of the socio-emotional domain of the V-RQOL.

There was no significant difference of Oral cavity D_{max}, D_{mean} and D_{max_1cc} at the end of radiation therapy, between V-RQOL total score groups (p= 0.682, 0.869 and 0.535 respectively), V-RQOL physical score groups (0.113, 0.186 and 0.182 respectively) and socioemotional score groups (0.121, 0.250 and 0.280 respectively).

Discussion

In IMRT for non-laryngeal head and neck cancers, various dose-volume parameters of radiation should be kept below a particular value for reducing the risk of laryngeal oedema and better voice quality.

According to Sanguineti et al (39), the $\mathbf{D_{mean}}$<43.5 Gy reduces the risk of grade 2 laryngeal oedema.

Fung (51) showed that mean laryngeal dose of 50 Gy received during radical RT in a group of patients with non-laryngeal cancers, had increased supraglottic activity, phase asymmetry and posterior glottic gap during video stroboscopic assessment.

Rancati et al(64) elucidated the D_{mean} to the uninvolved larynx (i.e. in non-laryngeal cancers) to minimize the risk of laryngeal oedema has to be kept <40 to 45 Gy by various NTCP models. The D_{mean} for involved larynx has to be kept below 63 to 66 Gy if possible.

LM D'Souza Lawrence et al(66) showed that D_{mean} to the larynx calculated as BED_3 showed a trend for correlation with laryngeal oedema.

As per the results of the present study, the mean laryngeal dose was 45.10 ± 14.14 Gy.

A D_{mean} of 4761.15 cGy was observed among all those who had grade 2 laryngeal oedema, while those who received a lower D_{mean} dose of 4473.58 had only grade 1 oedema.

JS Bae et al(65) compared the percentage of patients with laryngeal oedema with **D_{max}** more than and less than a value of 68 Gy. 50% of patients aged ≤ 68 years had grade ≥ 2 laryngeal oedema but, for > 68 years population the same was found to be 41% only.

From the analysis from our study, we found out that the mean D_{max} was 6266 cGy. The D_{max} for those with grade 2 oedema was 6659.7 cGy, while the same for those with grade 1 laryngeal oedema was 6224.5 cGy.

Sanguineti(39) has suggested the use of **V_{50}** < 27%, as a constraint for laryngeal sparing in IMRT plans as a better alternative than D_{mean} < 43.5 Gy. This is because it provides a more specific statement about the dose-volume relationship than the mean dose.

The findings in the present study is that mean V_{55} was 32.09% in patients with grade 2 oedema while it was 30.6% in those with grade 1. A dose-volume constraint for V_{55} was not deduced by ROC curves, because the difference between groups with grade 2 versus 1 oedema was not statistically significant. The risk of grade 2 oedema was less when the V_{65} was < 1% (sensitivity 78%, specificity 41% and AUC 62%).

The **mean** radiation dose delivered was 72 Gy in Fung et al (69). The mean total V-RQOL score, socioemotional score and physical score among these patients were 80.3, 85.5 and 76.9 respectively.

In Vainshtein et al(44), the mean glottic dose was 33.7 Gy, and it was shown that the OR was 1.081; 95% CI 1.046 - 1.116 with a $p < 0.001$ for the mean glottic dose with the voice-related quality of life assessed with HNQOL-C on multivariate analysis.

The mean radiation dose delivered in our cohort was 67.54± 3.96 Gy. The mean laryngeal dose among those with a V-RQOL total score <75 was 4640 cGy, while those with excellent quality of life with a score>75 had a lower D_{mean} of 4353 cGy. There was no statistically significant difference. The D_{mean} showed a similar difference when the V-RQOL score was stratified into two groups as <75 and >75 for the socioemotional (4856.8 cGy and 4185.8 cGy respectively) and the physical (4622.69 cGy and 3927.12 cGy respectively) domains also.

Dornfield(67) showed that when $\mathbf{D_{max}}$ was > 66 Gy to the larynx, there was a steep fall in the HNCI quality of life index. He assessed D_{max} at various points and the ones significant were in the lower lateral pharyngeal wall, false cords and AE fold.

Though a different questionnaire is used, the results are consistent with ours which showed that a mean D_{max} of 6067.3 cGy was observed for those with a V-RQOL socioemotional score more than 75, while those with less than 75 had a D_{max} of 6478.4 cGy. The D_{max} values for V-RQOL physical scores were 5974.4 cGy for those with a score of more than 75 and 6322.4 cGy for those with a score of less than 75.

The only evidence in the literature for comparison of voice-related quality of life with dose-volume parameters in a group of patients who have exclusively received IMRT

was Dornfield et al(67). He compares the quality of life with dose maximum at various critical points, while still there is no mention of any volume parameters.

The analysis of our data revealed that the mean percentage of the volume of larynx V_d receiving a particular dose, "d" (ranging from 5 Gy to 70 Gy) was less for those with a V-RQOL score > 75 than those with a V-RQOL score <75 for total, socio-emotional and physical domains. This difference between V_d for the 2 groups was significant only for V_{60}, V_{65} and V_{70} for the total score, V_{65} alone for the physical domain and V_5 to V_{70} for the socio-emotional domain.

In Sanguineti et al (39), univariate analysis of age with laryngeal oedema resulted in an odds ratio of 1.0 with 95% CI of 0.97 to 1.04, p=0.90. Bae (65) also showed that age was not a predictor of laryngeal oedema.

LM D'Souza Lawrence et al (66) showed that the age directly correlated with the laryngeal swelling in those with laryngeal volume change from baseline above the second tertile i.e. more than 20.6%.

Vainshtein et al (44) have shown the non-significance of age with the voice-related quality of life.

The median age of patients in our study was 46 years. It is evident that the patients in our study were much younger comparatively.

The incidence of laryngeal oedema or V-RQOL scores did not change significantly with age in the present study.

As per Lawrence D'Souza et al (66), increased laryngeal volume at planning was the only predictor of laryngeal oedema. Patients with baseline larger laryngeal volumes are less likely to show a relative volumetric change. The correlation of laryngeal volume with laryngeal oedema was present on multivariate analysis also confirming it as a strong predictor of laryngeal oedema.

The mean laryngeal volume in our patients were 12.5538 cm^3. Those with grade 2 oedema had an average volume of 13.4908 cm^3 while those with grade 1 oedema had a smaller mean laryngeal volume 12.4478 cm^3. But there was no statistically significant association between laryngeal volume and laryngeal oedema or V-RQOL score groups.

In Sanguineti et al (39), 12% of patients received chemotherapy, and the odds ratio of association with laryngeal oedema was 1.69 (0.76-3.77) with p=0.19.

But J S Bae(65) et al published that only 34% of those without chemotherapy had significant laryngeal oedema, but those who received chemotherapy had an incidence of 56%.

In our study, neither did those patients who underwent neoadjuvant chemotherapy had a significantly lower V-RQOL total score at the end of radiation therapy as compared to those who did not (71.18 versus 65.63) nor was there any significant difference in laryngeal oedema grades between them.

Sanguineti et al(39) showed that the weight loss during RT had an OR of 0.99 with 95% CI of 0.92 to 1.07 on univariate analysis for laryngeal oedema, which was not significant. Our results also showed no significant correlation between weight loss during RT and laryngeal oedema or voice-related quality of life.

Sanguineti (39) did not show any statistical difference for oropharynx site versus other sites. (OR 1.11; 95% CI: 0.98 to 1.26)

Bae et al (65) showed that only 37% of those with laryngeal primary had grade 2 or more laryngeal oedema, but this was 57% for those with a hypopharyngeal primary. p value was 0.001 on univariate analysis but was not significant in multivariate analysis. But T classification was an independent predictor in the multivariate analysis also ($p<0.001$).

In Fung et al (51), the non-laryngeal group had worse VHI scores as compared to those with the laryngeal primary. The VHI score was 25.76 versus 12.56. In Vainshtein et al, HNQOL-C scores of patients with a primary tumour in Tonsil versus base of tongue did not show any statistically significant ($p=0.1804$) difference.

The patients were grouped into nasopharynx, oropharynx and others in the present study, and this did not yield any significant difference between them regarding laryngeal oedema or V-RQOL.

In Sanguineti et al (39), there was an increased risk of 2.85 for N+ patients for laryngeal oedema ($p=0.02$).

JS Bae et al (65) had shown that there was a significant difference ($p<0.001$) of laryngeal oedema between those with N0 and N1-3 status (31% versus 63%).

Vainshtein et al (44) showed that there was no difference in HNQOL-C scores between node negative and positive patients ($p=0.1022$)

Contrary to what was expected, in the present study, 54.2 % of those who were node positive had a V-RQOL score<75, but 57.1% of those with node-negative patients had a score<75.

Oral cavity including tongue has an important role in speech delivery, and in turn is intermingled when assessing the voice-related quality of life.

Dornfield et al (67) showed that the dose to the base of tongue did not affect the speech-related quality of life. The p-value of the Pearson correlation coefficient between the doses at various points versus the speech-related quality of life was 0.41 and 0.56 for right superior base of tongue (RSBOT) and left the superior base of tongue (LSBOT) respectively.

There was no association of laryngeal oedema with oral mucositis grades 3 and 4 versus grades 1 and 2 in Sanguineti's study.

The results of our study showed a good correlation of oral cavity dose with the V-RQOL score at midway during radiation therapy. The difference between D_{max_1cc} was significant among those with V-RQOL total, socio-emotional and physical scores <75 (non-excellent) versus > 75 (excellent) groups, midway during RT. The D_{mean} significantly differed between only the V-RQOL total and physical scores < 75 and

>75 groups midway during RT. There was no correlation seen for oral cavity dose between groups at end of radiation therapy.

Limitations

(1) If a larger number of patients were included in our study, the difference in laryngoscopy grades and quality of life scores with differing radiation dose and volumes would have become probably statistically significant.

(2) Assessment of laryngeal oedema if done with videostroboscopy would be more sensitive in detecting the vocal cord changes rather than the fibre-optic laryngoscopy.

(3) The heterogeneity among the education of different patients from different sociocultural backgrounds would have had an impact on the interpretation of the V-RQOL questionnaire.

Conclusion

In IMRT for non-laryngeal head and neck cancers, there is a direct relationship of high radiation dose per volume with resultant significant laryngeal mucosal oedema.

Any grade of laryngeal oedema (Grade ≥ 1) has an impact on the different domains of voice-related quality of life.

The different domains of V-RQOL were affected by the high radiation dose per volume of the larynx.

To reduce the severity of laryngeal mucosal oedema and to improve the different domains of voice-related quality of life, it is good to reduce the higher radiation dose per volume of the larynx ($\geq V_{60} < 1\%$) especially in IMRT for non-laryngeal head and neck cancers.

There was no significant correlation between laryngeal oedema or V-RQOL with different primary sites or nodal stage

Age, laryngeal volume, different chemotherapeutic modalities, weight loss and oral cavity dose were not found to have any correlation with laryngeal oedema or V-RQOL.

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Appendix-I (Institutional Ethical & Research Board approval letter)

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Anna Benjamin Pulimood, M.B.B.S., MD., Ph.D.,
Chairperson, Research Committee & Principal

Dr. Biju George, M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

November 14, 2016

Dr Nikhil S,
PG Registrar,
Department of Radiation Oncology,
Christian Medical College,
Vellore 632 004.

Sub: **Fluid Research Grant NEW PROPOSAL:**
Effects of Radiation Dose and Volume to the Larynx in Intensity Modulated Radiation Therapy of non-laryngeal head and neck malignancies
Dr Nikhil S, Employment Number: 21284, PG Registrar, Radiation Oncology, Dr Rajesh I. Employment Number: 20297, Associate professor, Dept of Radiation Oncology, Dr Subhashini John, Emp no: 04126, Professor and Head Unit II, Dr. Rajeev Michael, Professor, Dr. Reji Thomas, Professor, Dr. Rajan Sundaresan, Associate Professor, Department of ENT unit I, Dr. Manu Mathew, Senior Resident, Emp. no: 31366, Department of Medical Physics, Dept. of Radiation Oncology. Mr. Bijesh Yadav, Senior demonstrator, Department of Biostatistics.

Ref: IRB Min No: 10257 [OBSERVE] dated 05.09.2016

Dear Dr Nikhil S,

I enclose the following documents:-

1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Biju George, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. Biju George
Secretary (Ethics Committee)
Institutional Review Board

Dr. BIJU GEORGE
MBBS., MD., DM.,
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

Cc: Dr Rajesh I, Dept. of Radiotherapy, CMC, Vellore

1 of 4

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788, 2284481 E-mail: research@cmcvellore.ac.in

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Anna Benjamin Pulimood, M.B.B.S., MD., Ph.D.,
Chairperson, Research Committee & Principal

Dr. Biju George, M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

November 14, 2016

Dr Nikhil S,
PG Registrar,
Department of Radiation Oncology,
Christian Medical College,
Vellore 632 004.

Sub: **Fluid Research Grant NEW PROPOSAL:**
Effects of Radiation Dose and Volume to the Larynx in Intensity Modulated Radiation Therapy of non-laryngeal head and neck malignancies
Dr Nikhil S, Employment Number: 21284, PG Registrar, Radiation Oncology, Dr Rajesh I. Employment Number: 20297, Associate professor, Dept of Radiation Oncology, Dr Subhashini John, Emp no: 04126, Professor and Head Unit II, Dr. Rajeev Michael, Professor, Dr. Reji Thomas, Professor, Dr. Rajan Sundaresan, Associate Professor, Department of ENT unit I, Dr. Manu Mathew, Senior Resident, Emp. no: 31366, Department of Medical Physics, Dept. of Radiation Oncology. Mr. Bijesh Yadav, Senior demonstrator, Department of Biostatistics.

Ref: IRB Min No: 10257 [OBSERVE] dated 05.09.2016

Dear Dr Nikhil S,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "Effects of Radiation Dose and Volume to the Larynx in Intensity Modulated Radiation Therapy of non-laryngeal head and neck malignancies" on September 05th 2016.

The Committee reviewed the following documents:

1. IRB Application format
2. Consent forms and Iinformation sheets
3. Cvs of Drs. Rajan Sundaresan, Rajiv, Subhashini, Manu Mathew, Nikhil and Rajesh.
4. Questionnaire (English, Tamil, Hindi)
5. No.of documents 1 - 4

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294. 2284202 Fax: 0416 – 2262788, 228448 E-mail: research@cmcvellore.ac.in

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Anna Benjamin Pulimood, M.B.B.S., MD., Ph.D.,
Chairperson, Research Committee & Principal

Dr. Biju George, M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on September 05th 2016 in the C K Job Hall, Paul Brand Building, Christian Medical College, Bagayam, Vellore 632002.

Name	Qualification	Designation	Affiliation
Dr. Biju George	MBBS, MD, DM	Professor, Haematology, Research), Additional Vice Principal , Deputy Chairperson (Research Committee), Member Secretary (Ethics Committee), IRB, CMC,Vellore	Internal, Clinician
Dr. B. J. Prashantham	MA(Counseling Psychology), MA (Theology), Dr. Min (Clinical Counselling)	Chairperson, Ethics Committee, IRB. Director, Christian Counseling Centre, Vellore	External, Social Scientist
Dr. Anuradha Rose	MBBS, MD, MHSC (Bioethics)	Associate Professor, Community Health, CMC, Vellore	Internal, Clinician
Dr. Jayaprakash Muliyil	BSc, MBBS, MD, MPH, Dr PH (Epid), DMHC	Retired Professor, Vellore	External, Scientist &Epidemiologist
Rev. Joseph Devaraj	BSc, BD	Chaplaincy Department, CMC, Vellore	Internal, Social Scientist
Mr. C. Sampath	BSc, BL	Advocate, Vellore	External, Legal Expert
Dr. Visalakshi. J	MPH, PhD	Lecturer, Biostatistics, CMC, Vellore	Internal, Statistician
Mrs. Sheela Durai	MSc Nursing	Professor, Medical Surgical Nursing, CMC, Vellore	Internal, Nurse
Ms. Grace Rebekha	M.Sc., (Biostatistics)	Lecturer, Biostatistics, CMC, Vellore	Internal, Statistician
Mrs. Pattabiraman	BSc, DSSA	Social Worker, Vellore	External, Lay Person
Dr. Rajesh Kannangai	MD, PhD.	Professor, Clinical Virology, CMC, Vellore	Internal, Clinician

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
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Director, Christian Counseling Center,
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Dr. Anna Benjamin Pulimood, M.B.B.S., MD., Ph.D.,
Chairperson, Research Committee & Principal

Dr. Biju George, M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

Dr. Balamugesh	MBBS, MD(Int Med), DM, FCCP (USA)	Professor, Pulmonary Medicine, CMC, Vellore	Internal, Clinician
Dr. SnehaVarkki	MBBS, DCH, DNB	Professor, Paediatrics, CMC, Vellore	Internal, Clinician
Mrs. Emily Daniel	MSc Nursing	Professor, Medical Surgical Nursing, CMC, Vellore	Internal, Nurse
Dr. Sathish	MBBS, MD, DCH	Professor, Child Health, CMC, Vellore	Internal, Clinician
Dr. Inian Samarasam	MS, FRCS, FRACS	Professor, Surgery, CMC, Vellore	Internal, Clinician
Dr. Mathew Joseph	MBBS, MCH	Professor, Neurosurgery, CMC, Vellore	Internal, Clinician
Dr. Ranjith K Moorthy	MBBS, MCh	Professor, Neurological Sciences, CMC, Vellore	Internal, Clinician

We approve the project to be conducted as presented.

Kindly provide the total number of patients enrolled in your study and the total number of withdrawals for the study entitled: "Effects of Radiation Dose and Volume to the Larynx in Intensity Modulated Radiation Therapy of non-laryngeal head and neck malignancies" on a monthly basis. Please send copies of this to the Research Office (research@cmcvellore.ac.in).

Fluid Grant Allocation:

A sum of 34,955/- INR (Rupees Thirty Four Thousand Nine hundred and Fifty five Only) will be granted for 24 Months.

Yours sincerely,

Dr. Biju George
Secretary (Ethics Committee)
Institutional Review Board

Dr. BIJU GEORGE
MBBS., MD., DM.
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

IRB Min No: 10257 [OBSERVE] dated 05.09.2016

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Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788, 2284481 E-mail: research@cmcvellore.ac.in

Appendix-II

Appendix- II (Clinical Performa for data collection)

Name: Hosp.No. R.T. No.

Age : DOB: Sex:

Address.

Local Permanent

Ph no Ph no

Socioeconomic status: 1. Patient's Occupation :

2. Patient's Education :

Presenting complaints:

	Y/N	Duration
Throat pain		
Dysphagia(liquids/semisolids/solids)		
Hoarseness		
Cough		
Stridor		
Neck swelling:		
Headache :		
Others:		

Addictions:

1. Smoking Y/N Number per day- Duration - /yrs 2. Smokless Tobacco Y/N Duration - /yrs

Type:

3. Alcohol Y/N Amount & frequency - Duration - /yrs

Associated diseases: Premalignant conditions

DM/ HT/ TB/ Others

Allergies

Past history: Previous malignancies

Surgeries

major illness

Drug history:

Treatment History: Surgery(Elsewhere/ At CMCH)-

Radiotherapy(Elsewhere/ At CMCH)-

Chemotherapy(Elsewhere/ At CMCH)-

Family history-

GENERAL EXAMINATIONS:

Performance status: ECOG

Physical parameters :Weight- Height- BSA-

Vitals :BP- PR-

Pallor/ Icterus/ Edema

Stridor/ Tracheostomy / Ryles tube

Systemic examination: CVS

RS

Abdomen

Local examination:

NPL scopy /IDL Sopy

Neck-

Lymphnodes-Y/N

Side	Level	no	Size	Mobile/ Fixed	Discrete/ Matted	Skin –Free/ Tethered Ulcerated
right	1					
	2					
	3					
	4					
	5					

left	1					
	2					
	3					
	4					
	5					

Clinical Diagnosis:

Site: **T** **N** **M** **Stage:**

INVESTIGATIONS

Haemogram (date:) HB- PCV- MCV-

TC- DC - Platelets-

Biochemistry (date:) Creatinine- Creatinine clearance –

LFT-

Na - K - Ca - Mg –

Virology (date:) HIV- HCV- HbsAg-

Chest xray (date:) -

Ultrasonogram (date:) -

Barium swallow (date:) -

Upper GI Scopy (date:) –

CT scan (date:) -

Histopathology Biopsy No (/)- Specimen No(/)-(date:) Squamous cell carcinoma / others –

Well / Moderately / poorly differentiated

Margins –

Lymphnodes: No- extracapsular invasion: Y/N

Lymphatic / vascular invasion - Y/N

FNAC: Site - Report -

(date:)

Final diagnosis

Site T N M Stage

Sub Site

TREATMENT DETAILS : CONVENTIONAL

EXTERNAL RT- Preoperative/ Post-operative/ Radical/ Palliative.

Overall treatment time:

Date started:

Date completed:

Machine:Co 60 / 6X / 15X.

Dose

Site	primary	+ve Nodes	Prophylactic nodes	Lower neck	Posterior neck
Dose					

Fractions / week:

Technique:

TD / #

Treatment Break Yes/No

No of breaks	Duration in days	Reason
1		
2		
3		
4		

Field size

SAD/SSD

Spine shielding- Y/N At ---------Gy

Separation at three level: 1- 2- 3- Calculation done for------ separation

Posterior Neck Electron energy: Rt - Lt-

<u>BRACHYTHERAPY:</u>

Dose :

Dose Rate: HDR / LDR

Technique:

No of weeks after EBRT:

Appendix III (V-RQOL Questionnaire)

VOICE RELATED QUALITY OF LIFE (V-RQOL) MEASURE

Name _____

Date _____

We are trying to learn more about how a voice problem can affect your day-to-day activities. On this paper you will find a list of voice related problems. Please answer all questions based upon what your voice was like over the past 2 weeks. There are no right or wrong answers.

Considering both how severe the problem is when you get it, and how frequently it happens, please rate each item below on how bad it is. (i.e. the amount of each problem that you have). Use the following scale to rate the amount of problem you have.

1= none, not a problem

2= a small amount

3= a moderate (medium) amount

4= a lot

5= Problem is “as bad as it can be”

Because of my voice, how much of a problem is this?

1. I have trouble speaking loudly or being heard in noisy situations 1 2 3 4 5

2. I run out of air and need to take frequent breaths while talking 1 2 3 4 5

3. I sometimes do not know what will come out when I begin speaking

1 2 3 4 5

4. I am sometimes anxious or frustrated because of my voice 1 2 3 4 5

5. I sometimes get depressed because of my voice 1 2 3 4 5

6. I have trouble using the telephone (because of my voice) 1 2 3 4 5

7. I have trouble doing my job or practising my profession(because of my voice)

1 2 3 4 5

8. I avoid going out usually (because of my voice) 1 2 3 4 5

9. I have to repeat myself to be understood 1 2 3 4 5

10. I have become less outgoing (because of my voice) 1 2 3 4 5

Appendix-IV (V-RQOL scoring methods)

Scoring Algorithm for V-RQOL Measure

V-RQOL General Scoring Algorithm

$$100 - \frac{(\text{Raw Score} - \#\text{ items in domain or total}) \times 100)}{(\text{Highest Possible Raw Score} - \#\text{ items})}$$

Social-Emotional Domain (Items 4, 5, 8, 10)

$$100 - \frac{(\text{Raw Score} - 4) \times 100)}{16}$$

Physical Functioning Domain (Items 1, 2, 3, 6, 7, 9)

$$100 - \frac{(\text{Raw Score} - 6) \times 100)}{24}$$

Total Score (Items 1-10)

$$100 - \frac{(\text{Raw Score} - 10) \times 100)}{40}$$

Example for Total Score

If *Raw Score is 30* (such as if a "medium problem" exists with all items), then:

$$100 - \frac{(20) \times 100)}{40}$$

$$= 100 - (0.5 \times 100) = 100 - 50 = 50 \textit{ Standard Score}$$

Appendix V (RTOG grading of laryngeal oedema)

RTOG Grade	Description
0	No oedema

1	Slight oedema = ‘‘minimal’’ thickening of the epiglottis, aryepiglottic folds, arytenoids, and false cords
2	Moderate oedema = more diffuse and evident oedema, although still without significant or symptomatic airway obstruction
3	Severe oedema = Significant airway obstruction
4	Necrosis

Appendix VI (Informed consent)

INFORMATION SHEET

Study title: **Effect of Radiation Dose and Volume to the Larynx in Intensity Modulated Radiation Therapy of non-laryngeal head and neck malignancies.**

The head and neck cancers account for one-third of cancers in the country. According to the Indian Council of Medical Research (ICMR), 0.2 to 0.25 million patients are diagnosed each year with head and neck cancers. The main modalities of treatment for the cure of head and neck cancers include surgery, radiation therapy and/or chemotherapy.

The radiation therapy of head and neck cancers result in many quality of life issues related to skin reactions, mucositis, dryness of mouth, difficulty in swallowing, speech and voice issues. This is because radiation dose required for tumour control would cause acute and late normal tissue effects, thus worsening the quality of life of the patient. Intensity-modulated radiation therapy (IMRT) has a definite advantage in this setting. IMRT is based on computer-

optimized treatment planning and a computer-controlled treatment delivery system. This generates dose distributions that sharply conform to the tumour target while minimizing the dose delivered to the surrounding normal tissues. The simultaneous integrated boost (SIB) treatment would offer an additional radiobiological advantage in terms of lower dose per fraction to the normal tissues while delivering high dose per fraction to the target volume. In head and neck cancers, treatment can be accurately delivered with IMRT because it results in relative sparing of normal structures such as parotid glands, and also organ motion is virtually absent with proper immobilization.

This study aims at assessing the effects of IMRT on larynx in patients with cancers of the Head and neck other than the larynx. It also assesses the quality of life in patients undergoing radiation therapy for head and neck malignancies through a questionnaire.

You are being requested to participate in this study assessing the effects of radiation on larynx in IMRT and the quality of life issues.

If you take part what you will have to do?

You will have to undergo assessment by laryngoscopy prior to, midway and after completion of the radiation treatment. You will have to answer a questionnaire enquiring issues you face during radiation treatment at three of your visits- one before starting radiation treatment, one midway and one after the end of radiation treatment. The laryngoscopy done midway during the radiation treatment would be performed as an additional procedure to see the status of your voice box in between the treatment.

Can you withdraw from the study after it starts?

Yes. Your participation in the study is absolutely voluntary. If you withdraw from the study during the treatment, it will not affect your treatment in any way.

What are the benefits of this study?

The results of dose and volume constraints which should be maintained to reduce the toxicity to the larynx during radiation therapy, obtained from this study can be applied for treating patients with Head and neck malignancies in future. This would help to reduce the voice and speech problems to the patients taking radiation therapy to Head and neck.

Will your personal details be kept confidential?

Yes. The results of the study, when published in any journal, would not reveal your name or personal information in any form.

Will you have to bear any extra expenses because of your participation in this study?

No. The laryngoscopy procedure which is done midway during the radiation therapy is covered by the study fund. You will not have to pay for it.

For any further queries, you may please contact: (Address and phone number was provided)

Informed Consent form to participate in a research study

Study Title: Effect of Radiation Dose and Volume to the Larynx in Intensity Modulated Radiation Therapy of non-laryngeal head and neck malignancies.

Study Number: _____

Subject's Initials: _____

Subject's Name: _____

Date of Birth / Age: _____

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions. [ ]

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

(iii) I understand that the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree with this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for the scientific purpose(s). [ ]

(v) I agree to take part in the above study. [ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable

Date: _____/_____/_____

Signatory's Name: _____ Signature:

Representative: _____

Date: _____/_____/_____

Signatory's Name: _____

Signature of the Investigator: _____

Date: _____/_____/_____

Study Investigator's Name: _____

Signature or thumb impression of the Witness: _____

Date: _____/_____/_____

Name & Address of the Witness: _____

Appendix- VII (Master sheet)

Key for master sheet:

Gender: 1 – male, 2 – female

Ethnicity: 1- North East Indian 2- North Indian 3-South Indian 4 –Others

Smoking: 1-nil 2-yes

Alcohol: 1-nil 2-yes

Chewing tobacco: 1-nil 2-yes

Primary site: 1- Nasopharynx 2- sinonasal malignancy 3- oropharynx 4- oral cavity 5- olfactory neuroblastoma 6- maxilla 9-others

Histology: 1-Well differentiated squamous carcinoma 2-Moderately differentiated squamous carcinoma 3- Poorly differentiated squamous carcinoma 4- Poorly differentiated malignancy 5-Sinonasal adenocarcinoma 6- Adenocarcinoma 7- Neuroendocrine carcinoma 8- Undifferentiated 9-Adenoid cystic carcinoma 10- Others

T: 1-1, 2-2, 3-3, 4-4a, 5-4b

N: 1-1, 2-2a, 3-2b, 4-2c, 5-3

Stage: I-1, II-2, III-3, IVA-4, IVB-5

Hoarseness, Dysphagia, Nasal block, Ear block, Nasal bleed, Throat pain, Ulcer mouth, Neck swelling: 1-nil 2-yes

Diabetes, Hypertension, Surgeries: 1-nil 2-yes

ECOG performance status: 0-1, 1-2, 2-3, 3-4, 4-5

Pallor: 1-nil 2-yes

RT: 1- Postoperative, 2-Radical

Chemotherapy: 1-nil, 2 -Neoadjuvant, 3 -concurrent, 4- Neoadjuvant and concurrent chemoradiation therapy

Boost temporality: 1-SIB, 2-Sequential, 3- Single phase

RT dose: in centigray

No of fractions: Total number of fractions

dpf: Dose per fraction in cGy

Oedema grade: Baseline, midway and at End: 0-grade 0, 1- grade 1, 2- grade 2, 3-grade 3, and 4-grade 4

Laryngeal volume: reported in cubic centimetres (cc)

D_{max}: Maximum laryngeal dose to any point in the laryngeal volume reported in Centigray (cGy).

$D_{max\ (1cc):}$ Maximum laryngeal dose to any 1 cc of the laryngeal volume reported in Centigray (cGy).

Dmean: Mean laryngeal dose reported in Centigray (cGy).

V_d: Percentage of the volume of the larynx receiving a particular dose, d.